Paid Circulation, 25,079

HOSPITAL LIBRARY

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL—*Established 1828*

VOLUME 238 • JANUARY 1, 1948 • NUMBER 1

Anticoagulant Treatment of Postoperative Venous Thrombosis and Pulmonary Embolism 1
James A. Evans and John F. Dee

Thiouracil and Allied Drugs in Hyperthyroidism 6
Elmer C. Bartels

Neurologic Disturbances with Folic Acid Therapy 11
Philip F. Wagley

Lipemia Retinalis 16
Samuel Stearns, Eli Friedman, Maurice Lugitch and Sumner H. Hoffman

Medical Progress: The Toxemias of Pregnancy 18
Benjamin Tenney, Jr.

Case Records of the Massachusetts General Hospital 25

Editorials:

More Poliomyelitis Cripples 30

Shortage of Nurses 31

Liquidation of Emergency Maternity and Infant Care Program 32

Robert N. Nye Memorial Fund 32
Massachusetts Medical Society 32
Massachusetts Department of Public Health . 32
Miscellany 34

Correspondence 34
Book Reviews 35
Notices 36

Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879.

New (21st) Edition

American Illustrated Medical Dictionary

More than 2000 new words alone — now a living and necessary part of today's medical literature and language — are clearly and authoritatively defined in the **New (21st) Edition** of this standard medical dictionary. For the revision, every page was submitted to the closest scrutiny, and additions appear in every section — especially in the fields of tropical medicine; physics and nucleonics (covering medical application of radioactive isotopes); biochemistry and pharmacology (antibiotics, enzymes, vitamins, endocrines); and medical zoology and mycology.

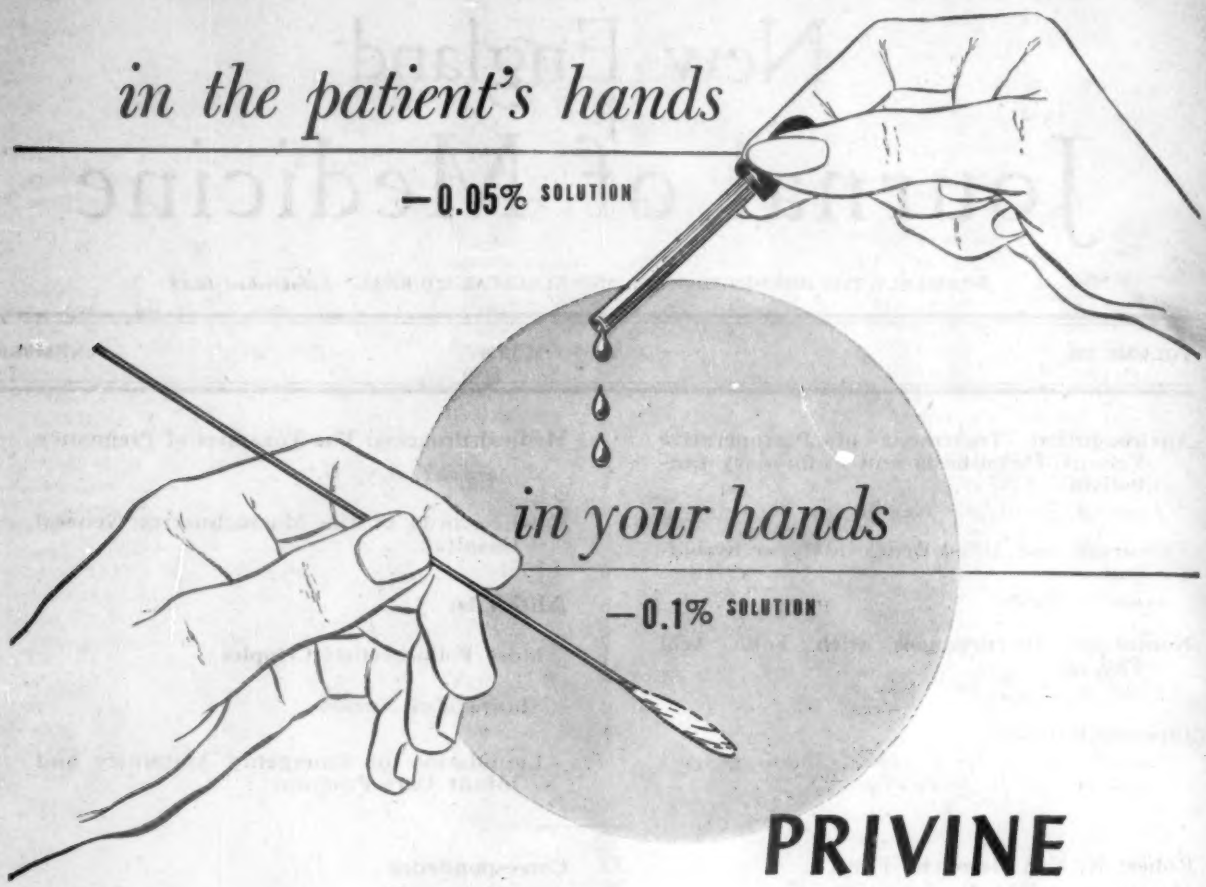
1660 pages, 6" x 9", with 880 illustrations, more than 100 in color. Flexible or stiff binding. Plain: $8.00; Thumb-indexed: $8.50.

W. B. Saunders COMPANY

WEST WASHINGTON SQUARE, PHILADELPHIA 5

in the patient's hands

—0.05% SOLUTION



in your hands

—0.1% SOLUTION

PRIVINE

PRIVINE hydrochloride, 0.05 per cent, is sufficiently potent to produce long-lasting relief in the average case of nasal congestion in patients of all ages. It is therefore the Privine preparation of choice for regular prescription purposes.

Privine hydrochloride, 0.1 per cent, fills the need for an agent which will produce the intense vasoconstriction frequently necessary for adequate visualization and for pre- and post-operative shrinkage. It is therefore the Privine preparation of choice for direct use in the office or hospital.

When properly administered, Privine hydrochloride induces prolonged vasoconstriction with relative freedom from local or general side effects. Three drops will usually produce nasal decongestion lasting 3–6 hours. Overdosage should be avoided.

Issued: 0.05%, bottles of 1 fl. oz. and 16 fl. ozs. • Jelly, 0.05%, tubes of 20 Gm.
0.1%, bottles of 16 fl. ozs. only

Ciba PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY

2/1328M

PRIVINE (brand of naphazoline) • *Trade-mark Reg. U. S. Pat. Off.*

The New England
Journal of Medicine

Copyright, 1948, by the Massachusetts Medical Society

Volume 238 JANUARY 1, 1948 Number 1

ANTICOAGULANT TREATMENT OF POSTOPERATIVE VENOUS THROMBOSIS AND PULMONARY EMBOLISM*

JAMES A. EVANS, M.D.,† AND JOHN F. DEE, M.D.‡

BOSTON

ANTICOAGULANT treatment is winning for itself a firm place in the armamentarium against postoperative venous thrombosis and pulmonary embolism. This has been accomplished by the sheer weight of accumulating statistics from various clinics, both in this country and in Sweden.[1–22] Since April, 1941, when dicumarol first became available, the drug has provided the predominant method of therapy at the Lahey Clinic. In the majority of cases a combination of heparin and dicumarol has been used. During the first four years heparin was given by continuous intravenous drip to cover the latent period of dicumarol. For the past two years deep injections of Loewe's[23,24] heparin in Pitkin menstruum§ have been given subcutaneously.

In this series of 184 cases, occurring from 1942-1946, venous ligation was also performed in 10 cases. The two systems of treatment, venous ligation and administration of heparin in Pitkin menstruum, should not be considered rival methods but rather complementary to each other. Our confidence in the efficacy of anticoagulant therapy, however, has grown through these five years to such an extent that the indications for venous ligation have dwindled to the following conditions: hemorrhagic disease; severe liver disease; second-stage operation; ambulatory phlebothrombosis with pulmonary embolism (Homans); resistance to both heparin and dicumarol; recurrence of benign embolism after supposedly adequate treatment; prophylactic ligation in patients over sixty years of age for expected bleeders (prostatic resection); and prophylactic ligation in patients over sixty who are debilitated from cancer or other causes (Miles resection). Ligation in elderly patients who are debilitated from cancer or other causes is regarded as only a relative indication to be used at the surgeon's judgment, because in the Lahey Clinic it would add the insurmountable surgical burden of about three or four thousand ligations a year. Therefore, prophylactic exercises, early ambulation and dicumarol prophylactically are preferred on the fourth day after operation.

Although it must be admitted that the vagaries of dicumarol resistance and sensitivity in different patients and the pitfalls of accurate prothrombin estimations should limit its use to the experienced and wary clinician equipped with a very reliable laboratory, it is believed that the advent of heparin in Pitkin menstruum will popularize anticoagulant therapy as a safe and reliable method of treatment. This will occur when the menstruum is more widely available and the cost of this product has dropped. Loewe[25] now claims that more careful buffering of the menstruum has overcome the frequent painfulness of the deposit in the tissues. This makes it possible to give more numerous injections than when heparin in Pitkin menstruum is combined with dicumarol. Up to the present time we have not had the opportunity of using this allegedly more painless formula. Unless the production of pain can be overcome, protracted treatment with many injections will be limited.

After five years' experience with anticoagulant therapy we have evolved the following set of rules — applicable to all patients kept lying in bed — for instruction to the staff:

> As a precaution against thrombosis and embolism, the patient should be instructed to wiggle the toes and feet one thousand times daily, including pressing the soles of the feet against the foot of bed if possible.
>
> If the patient has varicose veins, elastic bandages are to be used twenty-four hours a day until he is ambulatory.
>
> The patient should be asked daily on rounds if there is pain in the calf, and inspected for sore-

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1947.

From the Department of Internal Medicine, Lahey Clinic.

†Staff member, Department of Internal Medicine, Lahey Clinic.

‡Fellow in internal medicine, Lahey Clinic.

§Kindly supplied by W. R. Warner and Company, Inc., New York City, and in part by Roche-Organon, Nutley, New Jersey.

ness in the calf and for Homans's sign, especially if unexplained fever is present.

A stamp has been provided for history charts, entitled "History of Venous Thrombosis or Pulmonary Embolism." This should be stamped on every history and filled in. If a patient with such a history comes to surgery, he should receive postoperative anticoagulant therapy after consultation between the surgical and medical departments.

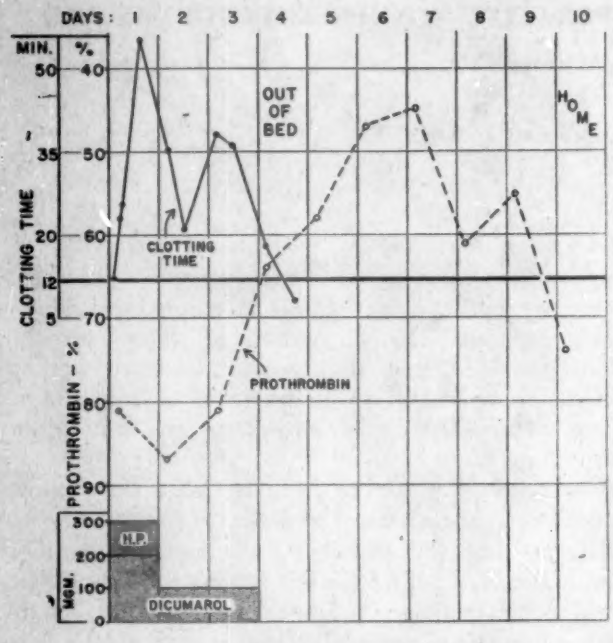


FIGURE 1. *Course in a Typical Case Successfully Treated with Anticoagulants.*

Any part of the coagulation time above the heavy black horizontal line represents the anticoagulant effect of heparin; any part of the prothrombin line above the same black line represents what is considered a fairly safe antithrombotic effect of dicumarol—namely, a prothrombin level below 65 per cent. We strive to keep the prothrombin percentage between 40 and 50.

Such treatment should be started routinely four days after operation, five days after gallbladder surgery or on a later day if deemed advisable by the surgeon. Dicumarol only is necessary for such prophylactic therapy, and therefore only the prothrombin time should be determined.

No anticoagulant therapy is given to patients with severe liver disease or hemorrhagic diseases or to those who are soon to undergo a second operation.

The routine after carotid-artery ligation, immediately after return from the operating room, includes 100 mg. of heparin in Pitkin menstruum without a vasoconstrictor, 100 mg. of heparin in Pitkin menstruum with a vasoconstrictor and 200 mg. of heparin in Pitkin menstruum with a vasoconstrictor if the patient weighs over 150 pounds. Only one such injection, deep subcutaneously, should be given, and no coagulation-time control is necessary.

For routine anticoagulant therapy, the prothrombin and coagulation times should be controlled.

Heparin in Pitkin menstruum — 100 mg. — without a vasoconstrictor and heparin in Pitkin menstruum — 100 mg. — with a vasoconstrictor should be injected deep subcutaneously; if the patient weighs over 150 pounds, 200 mg. with a vasoconstrictor should be injected deep in the subcutaneous tissues.

Dicumarol (200 mg.) should be given — 300 mg. if the patient weighs over 150 pounds.

Daily morning determinations of the coagulation time and prothrombin percentage are necessary.

A daily maintenance dose of 50 to 100 mg. of dicumarol should be administered to keep the prothrombin between 50 and 60 per cent.

No dicumarol should be given until the morning prothrombin time is known for that day.

If the patient proves refractory to dicumarol, the same dosage of heparin in Pitkin menstruum should be given until the coagulation time comes back to normal, usually every third day.

Heparin in Pitkin menstruum should be discontinued when the prothrombin drops to 60 per cent, and coagulation-time determinations should be stopped.

For any bleeding, the prothrombin time, as well as the coagulation time if the patient is also receiving heparin, should be determined, and 60 mg. of vitamin K given intravenously. This procedure is repeated every six hours until the prothrombin time is normal, which takes from eight to forty-eight hours. Fresh-blood transfusions should be given if indicated to give undeteriorated prothrombin. A transfusion is needed to counteract the effect of the heparin, and vitamin K to counteract that of dicumarol. Ice bags should be applied to the heparin in Pitkin menstruum deposit.

The patient is to be ambulatory when the temperature has returned to normal and local signs of venous thrombosis (except swelling) have disappeared, if the surgical department permits and if the anticoagulant effect is present.

Paravertebral sympathetic blocks should be employed if signs of reflex arterial spasm (swelling, white limb, absent pulses and pain) are present.

A heat cradle should be applied to the legs.

For pulmonary embolism, 0.6 to 0.12 gm. of papaverine should immediately be injected intravenously.

Figure 1 illustrates a typical successfully treated case. A majority of patients in this series were

allowed out of bed within ten days of the beginning of therapy.

The fact that anticoagulant therapy can do nothing to prevent the fragile red clot of phlebothrombosis from breaking off is the chief argument advanced by the opponents of this method of treatment. Three facts assure protection against this hazard: Loewe,[25] in a recent communication, has shown that heparin actually causes this "sludge" type of clot to disappear in animal experiments in vivo (whether dicumarol actually has a similar effect has never, to our knowledge, been proved); statistics have accumulated to prove that the actual subsequent pulmonary emboli to be expected statistically do not occur; and metastasis of the bland phlebothrombosis clot results from very fresh, unrecognized foci and rarely from clinically recognizable foci. Such dangerous new areas of phlebothrombosis are prevented from forming.

Death from pulmonary embolism is also made less likely by the prevention of propagation of a thrombus already present in the pulmonary arterial tree. This fact leads to the rule of permitting patients to be out of bed only when a good anticoagulant effect obtains.

The advantages of anticoagulation are as follows: avoidance of another operation, usually on a very sick patient; avoidance of danger of swelling in some cases; avoidance of danger of arterial thrombosis and gangrene in arteriosclerotic patients; inhibition of spreading thrombotic disease in systemic veins and in pulmonary arteries if a benign embolism has already occurred; no hesitation to institution of anticoagulant therapy in very doubtful cases; statistical proof from several clinics that anticoagulation prevents subsequent fatal pulmonary embolism; and decreased incidence of postphlebitic venous stasis and ulcer (Bauer[13]).

Results

There were 184 cases of postoperative venous thrombosis with or without pulmonary embolism during the five years 1942–1946. Sixty-three patients received heparin intravenously, 2 of them by the intermittent, Swedish method. Fifty-five received heparin in Pitkin menstruum. One to five injections of heparin in Pitkin menstruum were necessary according to the patient's refractoriness to dicumarol. Three patients received heparin only. Sixty-three patients received dicumarol only. Twenty-seven patients, or 15 per cent, were considered refractory to dicumarol. All such patients now receive heparin in Pitkin menstruum to keep them in control. A patient was considered refractory when the prothrombin level did not fall below 65 per cent despite ordinarily adequate doses. Fortunately, only 1 death occurred among the refractory patients, but this is not considered an excuse to administer dicumarol without adequate control of dosage by determination of the daily prothrombin levels.

Sixty-one of the 184 patients, or 33 per cent, had a warning benign pulmonary embolism (Table 1). To the 184 cases must be added 54 patients who had postoperative pulmonary embolism and who died untreated, because such deaths either occurred suddenly or were unrecognized as thrombosis with embolism. This makes a total of 238 cases of thromboembolic disease in five years, or an incidence of 0.42 per cent among approximately 56,000 major surgical operations performed at the New England Deaconess and New England Baptist hospitals by the surgeons of the Lahey Clinic. This low incidence

Table 1. *Incidence of Venous Thrombosis and Pulmonary Embolism among 56,000 Major Surgical Operations (1942–1946).*

Postoperative Complication	No. of Cases
Venous thrombosis without embolism (treated)	123
Venous thrombosis with warning pulmonary embolism (treated)	61
Sudden or unrecognized fatal pulmonary embolism (not treated)	54
Total	238 (0.42%)

was due to the assiduous care of the nursing staffs of these two hospitals in seeing that the patients carried out proper prophylactic exercises. That such precautions were largely responsible for the results is strongly suggested by the fact that in three winter months at the start of our campaign against pulmonary embolism the incidence in a hospital where the staff had not yet received instructions to carry out these exercises was three and a half times that in another hospital, where the exercises were practiced, the number of cases being 7 and 2 respectively.

There were 6 fatal cases in the series of 184 patients. Two were postoperative chemical deaths. One patient early in the series died of hemorrhage from dicumarol poisoning, because at that time the value of the rule never to give the daily dose of dicumarol until that morning's prothrombin time is known was not appreciated. This leaves 3 fatal cases of thromboembolic disease. One patient received inadequate doses of dicumarol, and a prothrombin level within the therapeutic range was never obtained; he was also given a transfusion, which destroyed any slight effect the dicumarol might have had, and he died of a second pulmonary embolism a few hours later. Another patient died a few hours after a single pulmonary embolism, in spite of one dose each of heparin in Pitkin menstruum and dicumarol given when he was *in extremis*. He would not have been saved by venous ligation, unless it had been done prophylactically at the time of operation. The cause of death in the

third case was declared sepsis by the pathologist. The patient had received adequate anticoagulant control throughout, but died of a septic infarct with pyopneumothorax and septic peritonitis.

It has long been recognized that a warning benign pulmonary embolism increases greatly the chance of a subsequent fatal embolism. In all 3 fatal cases a warning embolism had occurred. There were 61 cases in the series in which a warning was given by a benign infarct to the lung — a mortality of 5 per cent in this category, or 1.6 per cent for the entire series. In the past two years, since the use of heparin in Pitkin menstruum as well as dicumarol and with better control of the anticoagulant effect by continued administration of heparin subcutaneously until a good dicumarol effect is obtained, only 1 death has occurred—that of the patient with sepsis mentioned above.

There were benign recurrences of pulmonary embolism in 2 of the 61 patients who had warning benign pulmonary infarcts. One of these occurred after only four days and after treatment had been abandoned. Further heparin in Pitkin menstruum combined with dicumarol was given, with recovery. In the other patient dicumarol had also been stopped when a subsequent embolism occurred. Bilateral ligation was then performed, with recovery. The prothrombin level at the time of infarct was not stated in the records of either patient.

There was no occurrence of either fatal or benign pulmonary infarct among the 123 patients who never had a warning infarct. This fact points up the danger to the patient who has had a warning embolism.

TABLE 2. *Complications of Anticoagulant Therapy.*

COMPLICATION	NO. OF CASES
Serious bleeding requiring vitamin K or transfusions, or both, with recovery	4
Death from bleeding into wound from dicumarol poisoning	1
Epistaxis from ulcer on Hesselbach's triangle, requiring cauterization	1
Bleeding from various sources not requiring treatment	6
Total	12

TABLE 3. *Warning Signs in 52 Fatal Cases of Pulmonary Embolism (1940–1945).*

TYPE OF CASE	NO. OF CASES	WARNING SIGNS* NO. OF CASES
Death in 1 hour	22	16
Death in 2-24 hours	20	18
Death 1-24 days after first benign pulmonary embolism	10	10

*Warning signs included fever and tachycardia, varicose veins, previous history of thrombosis or embolism and premonitory pulmonary embolism.

COMPLICATIONS

Bleeding was recorded in 12 cases (Table 2). It was of a serious nature, requiring transfusions or vitamin K, or both, in 5. Two cases required heroic treatment with repeated doses of 60 mg. of vitamin K and transfusions totaling as much as 2750 cc. of blood. There was 1 fatal case of bleeding into the wound early in the series before vitamin K was known to be an antidote for dicumarol.

Vitamin K has made dicumarol much safer to use. For prothrombin levels as low as 20 per cent, we have often given booster doses of 40 mg. of vitamin K (either Hiquinone or Synkavite), bringing the prothrombin level to a safer therapeutic range but not losing the anticoagulant effect. For serious bleeding we recommend 60 mg. intravenously, repeated two or three times a day, together with transfusions of fresh citrated blood. Bank blood is too low in prothrombin content but may be used for blood replacement. We have had no experience with protamine as an antidote for heparin.

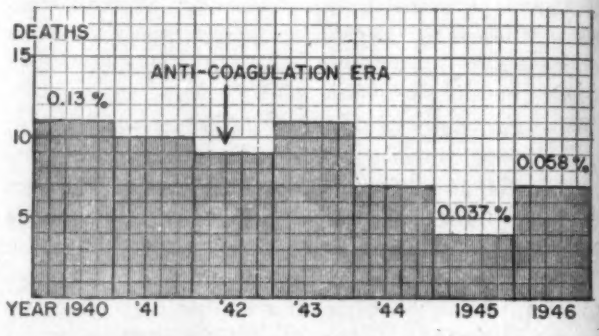


FIGURE 2. *Mortality from Postoperative Pulmonary Embolism. Note the decreasing rate after institution of anticoagulant therapy in 1942, together with institution of prophylactic exercises and increased watchfulness for signs of thromboembolic disease.*

There has been no incidence of hematomas at the site of injection of heparin in Pitkin menstruum in over 55 patients receiving eighty-three injections.

DISCUSSION

There still remains the problem of the sudden deaths from pulmonary embolism occurring before there is an opportunity to treat the patient. The results reported above give us great confidence in trusting anticoagulant therapy in the recognized cases of postoperative venous thrombosis. During the five years under study 59 patients died of pulmonary embolism; in 27 the diagnosis was proved at autopsy, 4 cases in this category occurring in medical patients. This situation must be met by eternal watchfulness of the postoperative and bed-

ridden patient. Here, too, lies a field for more prophylactic ligations as done by Allen, Linton and Donaldson[26] in the debilitated patient over sixty years of age. Dicumarol should be used prophylactically more often, and we give this treatment routinely to patients with a history of thrombophlebitis or embolism following a previous operation or childbirth. Our results in the prophylactic use of dicumarol will be the subject of a future report.

In addition to the routine daily examination of legs postoperatively, more attention must be paid to the temperature and pulse chart. A recent analysis of 52 cases of death from pulmonary embolism revealed that 85 per cent of the patients gave warning signs of rise in temperature or pulse, or both, or had varicose veins or a previous history of thrombotic disease (Table 3).[8]

That our efforts to prevent death from postoperative pulmonary embolism have not been in vain is shown in Figure 2. The mortality was cut to one fourth in 1945 and to one half in 1946. The rise during the last year shows the need of guarding against complacency and of still greater alertness on the part of all services to attain what should no longer be considered an impossibility: a deathless year from pulmonary embolism. More prophylaxis by both venous ligation and anticoagulation seems to be the answer. The former is impractical in a large surgical service except in cases considered most susceptible. Prophylactic exercises, bandaging of varicose veins, early ambulation and anticoagulant therapy must be used for the larger majority of patients considered to be susceptible. Anticoagulant therapy is adequate for postoperative patients who already have developed thrombosis with or without pulmonary embolism.

Summary

Anticoagulant treatment by heparin or heparin in Pitkin menstruum in combination with dicumarol offers a safe, practical method to prevent postoperative death from pulmonary embolism.

The recent introduction of heparin in Pitkin menstruum injected subcutaneously has greatly simplified anticoagulation. This therapy has the added advantage of producing an anticoagulative effect that can easily be kept up as long as necessary in the dicumarol-refractory patient.

Of 184 patients with postoperative venous thrombosis with or without warning pulmonary embolism, 3 patients died of thromboembolic disease — an incidence of 1.6 per cent. These 3 deaths occurred in the particularly dangerous group of cases in which the patients had already suffered one pulmonary embolism, and represented a mortality of only 5 per cent in this category. On analysis, none of these 3 cases presented a clear-cut argument against the efficacy of anticoagulation therapy.

Since 85 per cent of patients with fatal pulmonary emboli give warning signs, usually a low temperature and tachycardia or a history of previous thromboembolic disease, or have varicose veins, a plea is made for better prophylaxis. This can be accomplished by leg exercises, bandaging of limbs, early ambulation, prophylactic ligation in debilitated patients over sixty years of age or the administration of dicumarol on the fourth day after operation.

References

1. Evans, J. A. Combined use of heparin and dicoumarin (3,3′ methylenebis,4-hydroxycoumarin) in thrombophlebitis and pulmonary embolism (preliminary report). *Lahey Clin. Bull.* **2**:248-256, 1942.
2. *Idem.* Orientation of treatment in thrombophlebitis, phlebothrombosis and pulmonary embolism. *Ann. Int. Med.* **17**:970-974, 1942.
3. *Idem.* Indications for treatment of thrombophlebitis, phlebothrombosis and pulmonary embolism. *S. Clin. North America* **22**:945-963, 1942.
4. *Idem.* Dicumarol therapy in thrombotic emergencies. *New Eng. J. Med.* **230**:131-135, 1944.
5. *Idem.* Problems of postoperative thrombophlebitis and pulmonary embolism. *Connecticut M. J.* **8**:71-75, 1944.
6. *Idem.* Anticoagulation therapy of postoperative venous thrombosis and pulmonary embolism. *S. Clin. North America* **24**:534-537, 1944.
7. Evans, J. A., and Kassell, M. B. Thrombophlebitis and pulmonary embolism in pelvic surgery. *S. Clin. North America* **25**:601-608, 1945.
8. Evans, J. A., and Boller, R. J. Prevention of death from postoperative pulmonary embolism. *Lahey Clin. Bull.* **5**:10-12, 1946, and *New Eng. J. Med.* **236**:392-397, 1947.
9. Allen, E. V. Challenge of thrombosis and embolism of blood vessels. *Proc. Staff Meet., Mayo Clin.* **20**:302-306, 1945.
10. Barker, N. W., Allen, E. V., and Waugh, J. M. Use of dicumarol [3,3′ methylenebis (4-hydroxycoumarin)] in prevention of postoperative thrombophlebitis and pulmonary embolism. *Proc. Staff Meet., Mayo Clin.* **18**:102-107, 1943.
11. Barker, N. W., Cromer, H. E., Hurn, M., and Waugh, J. M. Use of dicumarol in prevention of postoperative thrombosis and embolism with special reference to dosage and safe administration. *Surgery* **17**:207-217, 1945.
12. Barker, N. W. Clinical use of dicumarol. *M. Clin. North America* **29**: 929-935, 1945.
13. Bauer, G. Heparin therapy in acute deep venous thrombosis. *J. A. M. A.* **131**:196-203, 1946.
14. Bruzelius, S. Dicoumarin in clinical use: studies on its prophylactic and therapeutic value in treatment of thrombo-embolism. *Acta chir. Scandinav.* (Supp. 100) **92**:1-219, 1945.
15. Murray, G. D. W., and Best, C. H. Use of heparin in thrombosis. *Ann. Surg.* **108**:163-177, 1938.
16. Prandoni, A., and Wright, I. Anti-coagulants: heparin and dicoumarin — 3,3′ methylene-bis-(4-hydroxycoumarin). *Bull. New York Acad. Med.* **18**:433-458, 1942.
17. Wright, I., and Prandoni, A. Dicoumarin 3,3′ methylene-bis-(4-hydroxy-coumarin): its pharmacologic and therapeutic action in man. *J. A. M. A.* **120**:1015-1021, 1942.
18. Duryee, A. W. Thrombophlebitis — medical treatment. *Bull. New York Acad. Med.* **20**:604-622, 1944.
19. Lehmann, J. Hypoprothrombinaemia produced by methylene-bis-(hydroxycoumarin): its use in thrombosis. *Lancet* **1**:318, 1942.
20. Murray, G., and MacKenzie, R. Postoperative thrombosis and embolism. *Am. J. Surg.* **57**:414-428, 1942.
21. Ottenheimer, E. J. Use of heparin and dicoumarin in treatment of thrombophlebitis. *New Zealand Med. J.* (Supp.), p. 12 April, 1943.
22. Zucker, H. D. Clinical experiences with dicumarol: report of 18 cases. *J. A. M. A.* **124**:217-220, 1944.
23. Loewe, L., Rosenblatt, P., and Lederer, M. New method of administering heparin. *Proc. Soc. Exper. Biol. & Med.* **50**:53-55, 1942.
24. Loewe, L., and Rosenblatt, P. New practical method for subcutaneous administration of heparin: preliminary report. *Am. J. M. Sc.* **208**: 54-63, 1944.
25. Loewe, L., Rosenblatt, P., and Hirsch, E. Venous thromboembolic disease. *J. A. M. A.* **130**:386-393, 1946.
26. Allen, A. W., Linton, R. R., and Donaldson, G. A. Venous thrombosis and pulmonary embolism. *J. A. M. A.* **133**:1268-1274, 1947.

THIOURACIL AND ALLIED DRUGS IN HYPERTHYROIDISM*

ELMER C. BARTELS, M.D.†

BOSTON

THE introduction by Astwood of new and potent antithyroid substances has permitted a great advance in the treatment of hyperthyroidism and has given a new tool with which to further knowledge of the pathological physiology of diseases of the thyroid gland. This report deals with the clinical application of these drugs, which are capable of reducing to normal the elevated basal metabolic rate of hyperthyroidism resulting from either primary hyperthyroidism or adenomatous goiter. With the fall in the basal metabolic rate there is gradual amelioration of all hyperthyroid signs and symptoms except those of the eye, if these signs are marked when therapy is begun. Those who have had experience with the use of thiouracil and allied drugs must now report their results so that proper evaluation can be made. Particularly, the early overoptimistic statements regarding their supposed curative properties must be assayed.

ACTION

When the drugs are administered in adequate doses, the production of thyroxin is halted as shown by a reduction in the blood protein-bound iodine and in the iodine content of the thyroid gland. The basal metabolic rate drops, and if the agent is continued sufficiently long, myxedema results and is maintained as long as the drug is given. Unlike the antithyroid action of iodine, which produces striking histologic improvement in the thyroid gland in primary hyperthyroidism with lessening of symptoms, thiouracil and its allied substances, although affording striking effects upon the clinical and metabolic picture, cause no change in the histologic picture. The hyperplasia of the thyroid gland may even increase. In determining whether or not these drugs will provide a substitute for subtotal thyroidectomy, it must be recognized that the histopathologic change (hyperplasia), which originally brings about hyperthyroidism, is still present even after the basal metabolic rate has been effectively restored to normal.

It was initially supposed that these drugs acted by preventing the thyroid gland from absorbing iodine. Clinical experience, however, revealed this to be incorrect, since it was found that the administration of Lugol's solution produced involution of the thyroid gland even when thiouracil was being administered. This was demonstrated by an increase in the firmness of the gland, a lessening or disappearance of the bruits and thrills at the superior poles and a marked reduction in the vascularity of the gland at operation in patients receiving Lugol's solution in conjunction with thiouracil. A comparison of patients receiving thiouracil alone and those receiving both thiouracil and iodine showed that there was substantially more iodine in the thyroid glands of the latter (Fig. 1). It was then reported by McGinty and Sharp[2] that the iodine absorbed by additional iodine feeding to rats receiving thiouracil or propylthiouracil is not synthesized into a protein-bound form but remains in the gland as iodide. This indicates that these antithyroid substances act by preventing the synthesis of iodide to an active protein-bound hormone — diiodotyrosine and thyroxin (Fig. 2). The thiocyanate ion, on the other hand, has a specific effect upon the thyroid gland in that it interferes with the mechanism that permits the gland to hold the iodide ion and does not seem to interfere with the synthesis of the thyroid hormone.[3]

The selective mechanism by which thiouracil and its allied substances interfere with the organic blending of iodide is as yet not certain. Studies by DeRobertis[4] warrant the conclusion that these substances probably act by inhibiting the peroxidase or enzymatic system in the thyroid gland that functions to oxidize iodide to form the protein-bound or active thyroxin molecule.

DOSAGE

The effective daily dose of thiouracil was established from the very outset to be 600 mg. Thiobarbital, which was next given a therapeutic trial, was found to affect the metabolism beneficially in a single dose of 50 mg. a day. The dose of propylthiouracil, which was initially suggested as 50 to 100 mg. daily, was found to be inadequate, since it did not produce a response comparable to that obtained with a daily dose of 600 mg. of thiouracil. Some patients responded to 75 mg. a day, but it was not until the daily dose had been increased to 200 mg. that uniformly satisfactory improvement was accomplished in all cases. Larger doses, up to 600 mg. a day, have been used in a few cases without a significant difference in clinical response to that obtained with 200 mg. For patients with large adenomatous goiters, whose response to therapy is always slow, a daily dose of 300 mg. is given.

Propylthiouracil, the drug that we now employ exclusively, is administered in a dosage of 100 mg.

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1947.

From the Department of Internal Medicine, Lahey Clinic.

†Member, Department of Internal Medicine, Lahey Clinic; staff member, New England Deaconess and New England Baptist hospitals.

every twelve hours (100 mg. at 8 a.m. and 100 mg. at 8 p.m.). In a few patients the entire dose, 200 mg., was administered once a day with a clinical response that was as effective as that to the divided doses.

Toxicity

Since the three agents with which we have had experience are equally effective in lowering the basal metabolic rate, the choice of agent for clinical use is dependent on the percentage of reactions to each. Of the three, thiobarbital had the highest incidence of complications, 28 per cent, thiouracil, 9 per cent, and propylthiouracil is much the safest, 1.6 per cent, or six reactions in 430 cases.

The reactions to thiouracil consisted of depression of the white-cell count, fever, swollen salivary glands, skin rash and edema of the skin, with 1 fatal case of agranulocytosis. Thiobarbital primarily affected the white-cell count and occasionally caused fever. The six definite reactions to propylthiouracil included depression of the white-cell elements in 5 patients and fever in 1; the blood changes were variable (Fig. 3), comprising granulocytopenia without leukopenia, or leukopenia without granulocytopenia and various degrees of depression of both the leukocytes and granulocytes. One patient developed agranulocytosis; this patient recovered after penicillin therapy. These experiences indicate that propylthiouracil is by far the safest drug but force the conclusion that it is not entirely unattended by significant side effects.

Remission and Relapse

It was hoped by all and prematurely reported as established by some that these new drugs had, in addition to the capacity to reduce the basal metabolic rate to normal, the property of producing a sustained remission of hyperthyroidism in a high percentage of patients. A year of continued therapy was suggested as a means of effecting the desired result. Wider experience by many physicians soon indicated that prompt relapse of hyperthyroidism followed a reduction of the dose or withdrawal of the drug in many cases, irrespective of the duration of active therapy. In other cases prolonged remissions occurred after discontinuance of treatment. The percentage of remissions produced and the percentage of relapses vary widely in the available reports. My experience indicates that prolonged remission (we prefer to designate the hyperthyroid-free period as remission and not cure) occurs in some patients with mild hyperthyroidism in whom

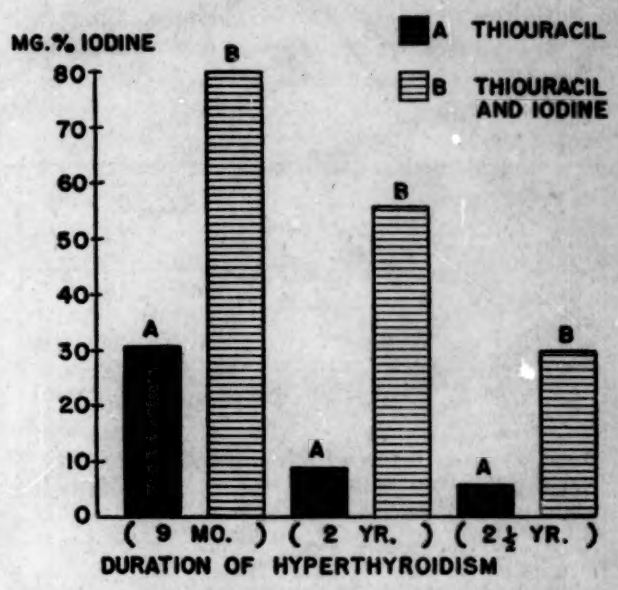


Figure 1. *Comparison of the Iodine Content of the Thyroid Gland following the Administration of Thiouracil with That following the Administration of Combined Thiouracil and Iodine (Reproduced from Lahey et al.[1] by Permission of the Publishers).*

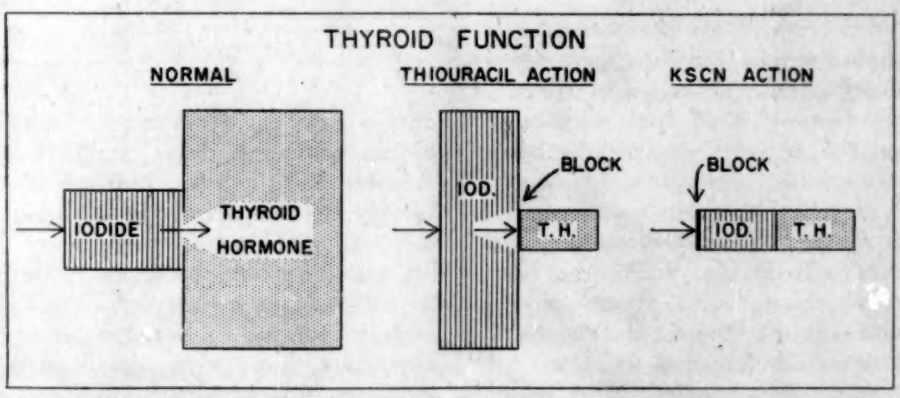


Figure 2. *Schematic Comparison of the Normal Thyroid Function as Affected by Thiouracil and Potassium Thiocyanate.*

the thyroid enlargement is but slight and that the duration of treatment has little to do with the duration of the remission so long as the basal metabolic rate is normal when the drug is withdrawn (Fig. 4). Likewise, relapse in two to six months was observed after reduction of the dose or on withdrawal of antithyroid therapy in patients with a high degree of hyperthyroidism and substantial thyroid enlargement, in spite of prolonged therapy (Fig. 5).

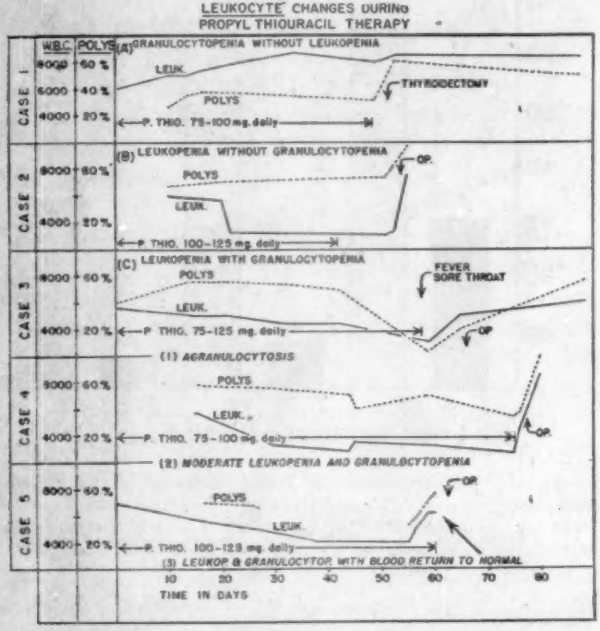


FIGURE 3. *Significant Changes in the Total White-Cell Count and Polymorphonuclear Percentage during the Administration of Propylthiouracil (Reproduced from Bartels[6] by Permission of the Publishers).*

Since a large proportion of the patients who are referred to the Lahey Clinic for care have severe hyperthyroidism, a program of treatment aimed at inciting a remission would hold little chance for success. Whether the recently suggested plan of producing hypothyroidism before withdrawal of treatment[7] will result in a higher percentage of remissions or in more prolonged remission, only further observation will decide. From the histopathological standpoint, since the enlarged thyroid gland is present and still hyperplastic and the adenomatous gland remains as before, it is expected that this plan would only delay the inevitable relapse that follows. It has been reported that prolonged treatment leads to exhaustion and atrophy of the thyroid gland. We have observed the gland to decrease in size in a few patients with mild hyperthyroidism with only slight thyroid enlargement who have remained in prolonged remission. We have also observed, however, substantial increases in the size of the thyroid gland of patients with primary hyperthyroidism and adenomatous goiter under antithyroid treatment. Actually, the basic etiologic cause of hyperthyroidism must be determined before the occurrence of relapse or remission of hyperthyroidism as affected by antithyroid therapy is understood.

Maintenance Therapy

The use of antithyroid drugs as maintenance treatment, which is necessary in a high percentage of cases if medical treatment is to be utilized and thyroidectomy avoided, carries with it certain specific disadvantages. It must, however, be admitted that by a carefully regulated daily dose of these drugs, hyperthyroidism can be adequately controlled for a prolonged period. Proper regulation entails periodic observations, which must include determination of basal metabolic rates and blood studies, and in the event of intercurrent illness further adjustment of the dose may become necessary, as with insulin therapy in diabetes. There are many serious objections to permitting patients to continue in a state of only partial control of hyperthyroidism, especially patients in the older age group, those with associated heart disease and those patients with psychotic tendencies. This fact must be emphasized since at present we are seeing a great many hyperthyroid patients whose disease is only partially controlled or with relapsing hyperthyroidism who can ill afford further systemic depletion. Complete control is not accomplished chiefly because of inadequate observation or understanding of antithyroid therapy on the part of the physician or the well recognized tendency of patients

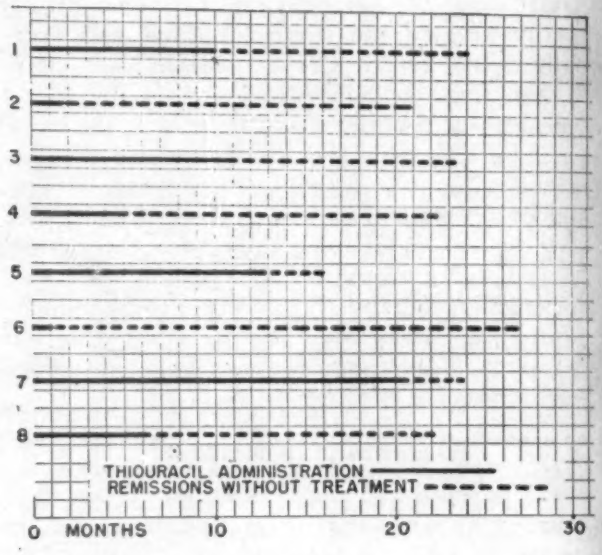


FIGURE 4. *Prolonged Remission after Treatment with Thiouracil in Mild Hyperthyroidism with Slight Thyroid Enlargement (Reproduced from Bartels[6] by Permission of the Publishers).*

to alter or discontinue therapy in the event that symptoms or signs appear that are unattributable to the medication that is being administered.

Other serious objections to maintenance treatment include such important factors as: failure to bring about cure of the hyperthyroidism; persistence of goiter; inherent dangers in not removing adenomatous goiters; possible reactions to the medication; and possible development of serious histopathological change in the thyroid gland.

All these objections must be given careful consideration when maintenance management is undertaken. Few patients are likely to choose prolonged treatment that in the end is not curative when a satisfactory surgical approach is available. The continued presence of the goiter, even though it is inactive, connotes potential trouble and indicates to the patient that he has not been cured of his disease. Over the years surgeons interested in thyroid disease have taught the advisability and urged the removal of adenomatous goiters, especially if single. Removal of such goiters seems necessary because of the possibility of malignant change, which some investigators have placed as high as 22 per cent.[8] With this knowledge added to other objections, including tracheal deviation and compression, it seems unwise to discard thyroidectomy in this type of goiter in which the results have been so completely satisfactory. The possibility of a reaction to the medication, although small, is real, and past experience has shown that there is no time during which one can feel entirely safe with their administration. Recent experimental work by Money and Rawson[9] on the prolonged use of thiouracil in rats has shown the development of cystadenomas in the thyroid gland, which appear to have malignant potentialities. Whether similar changes will occur in thyroid glands in human beings or whether administration of Lugol's solution mitigates the danger of these tumor formations is not known.

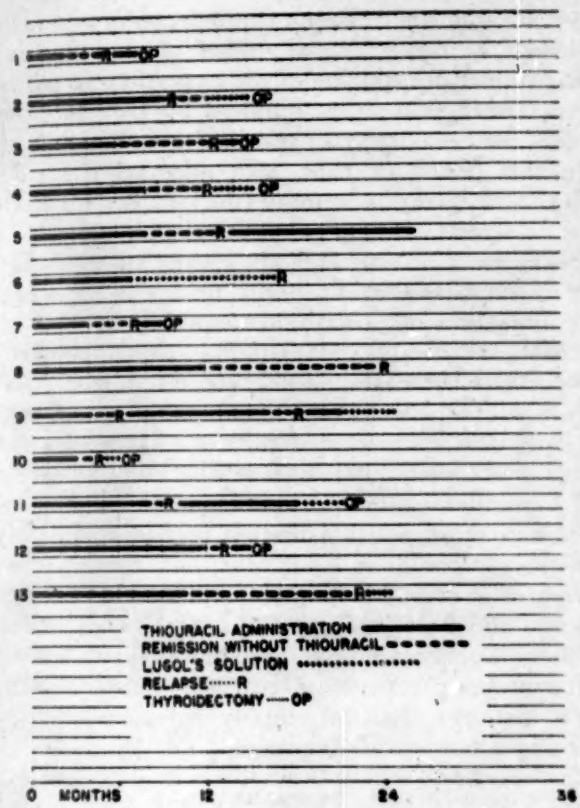


FIGURE 5. *Relapse of Hyperthyroidism after Treatment with Thiouracil in Severe Hyperthyroidism with Substantial Thyroid Enlargement (Reproduced from Bartels[6] by Permission of the Publishers).*

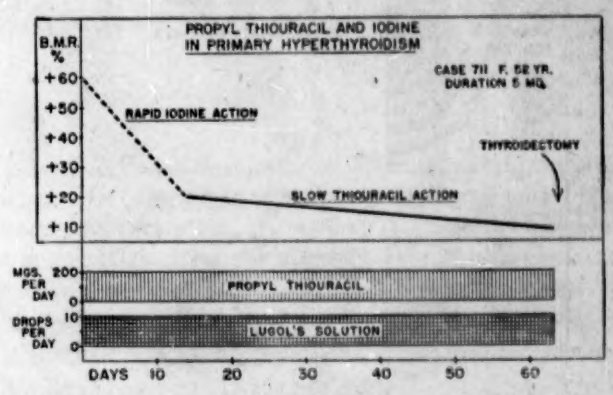


FIGURE 6. *Simultaneous Administration of Propylthiouracil and Lugol's Solution Producing Rapid Initial Drop in the Basal Metabolic Rate, Followed by a Slow Fall to Normal.*

ADJUNCT TO THYROIDECTOMY

Our chief experience with the antithyroid drugs has been in the field of preparing patients for thyroidectomy. It has been found that when treatment with these drugs is carefully managed, subtotal thyroidectomy can be carried out without risk, and hyperthyroid reactions during anesthesia and after operation, which in the past have caused great concern, are completely eliminated. Initially, only severely hyperthyroid patients were treated preoperatively with these drugs, but since propylthiouracil has been available an increasing number of such patients are receiving the drugs. Patients with milder hyperthyroidism, however, are still prepared with Lugol's solution alone.

When these drugs are employed as a preoperative agent it is essential that they be used until full benefit is obtained, which is indicated by complete relief of all hyperthyroid signs and symptoms and return of the basal metabolic rate to nearly normal. Furthermore, it is advisable to maintain certain

patients at a normal metabolic level for a month or more before proceeding with thyroidectomy. These include patients in the older age group, those with long-standing hyperthyroidism, especially owing to adenomatous goiter, those who have suffered great visceral depletion, thyrocardiac patients in whom it is advisable to restore the heart to normal compensation and reserve and patients with related or unrelated psychoses.

Early in our experience, Lugol's solution was given for three weeks before operation to overcome the vascularity of the thyroid gland that occurs with thiouracil treatment when patients with primary hyperthyroidism are prepared for thyroidectomy. Now patients receive propylthiouracil and iodine simultaneously from the beginning of treatment. With this new plan (Fig. 6), improvement starts promptly owing to the quick action of Lugol's solution, and through the action of propylthiouracil, improvement is sustained until full control of the hyperthyroidism is obtained. Iodine therapy, therefore, has two important functions: one of aiding in early clinical improvement, and the other of reducing the vascularity of the thyroid gland in preparation for easy thyroidectomy.

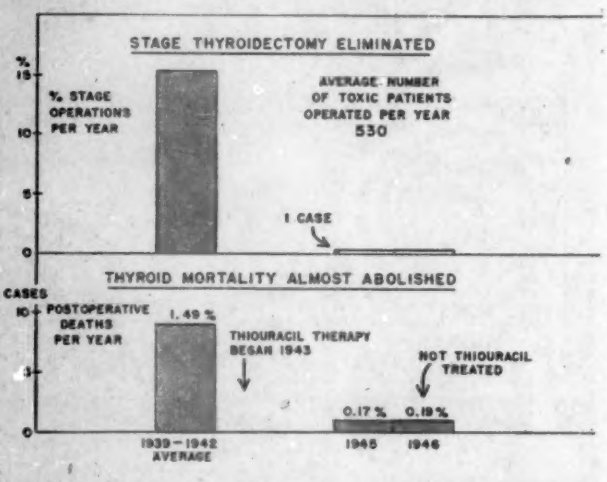


FIGURE 7. *Comparison of the Percentage of Hemithyroidectomies Done before and since the Use of Antithyroid Drugs (Also, the Decrease in the Operative Mortality from 1.42 to 0.12 per cent is Shown).*

The use of Lugol's solution with propylthiouracil from the onset* of therapy has delayed the ultimate recovery in that the average drop in the basal metabolic rate is now estimated as 1 per cent and 0.8 per cent as compared with 1.3 per cent and 1 per cent, respectively, in patients with hyperthyroidism of short duration and those with long-standing hyperthyroidism. The slowing effect of Lugol's solution, however, is not objectionable, since it is outweighed by the rapid clinical improvement. Patients with adenomatous goiter do not require iodine, and two days of treatment is required for each percentage of elevation of the basal metabolic rate.

In the last four years 830 patients have been prepared for thyroidectomy with antithyroid drugs, thiouracil being used in 381, thiobarbital in 28 and propylthiouracil in 421 patients. There was 1 death on the second postoperative day owing to coronary disease — an operative mortality of 0.12 per cent (Fig. 7) as compared with 1.49 per cent prior to the preoperative use of these drugs. Two-stage operations have been reduced from an average of 16 per cent to practically nil — only one such operation was done in 1946, and one so far in 1947.

Those who champion the medical treatment of hyperthyroidism condemn thyroidectomy as a useful procedure. We believe, as a result of our experience, that proper preparation of the hyperthyroid patient with antithyroid drugs followed by thyroidectomy offers the best chance of restoration to health in the shortest period of time with minimal risk. The objections to thyroidectomy (the incidence of tetany or unilateral vocal-cord paralysis should not be greater than 0.5 per cent) are usually surmountable. Of these two conditions, only tetany is admittedly an objectionable condition requiring careful and prolonged therapy. Myxedema, which occurs in 2 per cent of cases, is not greatly objectionable, since it can be easily and completely controlled by a daily dose of desiccated thyroid. Myxedema may actually be welcomed by those who fear a recurrence of hyperthyroidism. The recurrence rate after two years in those patients treated preoperatively with antithyroid drugs is 2 per cent; half these patients required reoperation for removal of thyroid remnants, and half obtained full control after a daily dose of Lugol's solution. Therefore, thyroidectomy after proper preoperative treatment resulted in cure in 95 per cent, with only tetany or recurrence representing a serious disadvantage.

SUMMARY

The new antithyroid drugs, if properly administered, will lower the basal metabolic rate of all patients with primary hyperthyroidism or adenomatous goiter with hyperthyroidism. All signs and symptoms of hyperthyroidism except prominence of the eyes subside, if present at the beginning of treatment.

Present information indicates that these drugs act on the thyroid gland by preventing the synthesis of stored iodide to an active protein-bound hormone.

The comparative effective daily doses of thiouracil and propylthiouracil are 600 mg. and 200 mg., respectively.

The toxicity incidence of thiouracil is 9 per cent, and that of propylthiouracil 1.6 per cent. Therefore, propylthiouracil is the drug of choice, but since it may affect the white-cell elements its use is not without danger.

*Further studies show that patients who have primary hyperthyroidism with large goiters should be treated by the old plan since response to therapy may be indefinitely delayed by the use of both Lugol's solution and propylthiouracil from the beginning of treatment.

Prolonged remission of hyperthyroidism after antithyroid treatment may occur in cases of mild hyperthyroidism with slight thyroid enlargement. In cases of severe hyperthyroidism with sizable goiters the incidence of prolonged remission is low.

Maintenance therapy with antithyroid drugs is possible, but this type of treatment has some objections, including certain definite risks.

As preoperative adjuncts to thyroidectomy these new drugs have filled a great need and if properly used permit the elimination of operative reactions and mortality.

References

1. Lahey, F. H., Bartels, E. C., Warren, S., and Meissner, W. A. Thiouracil — its use in preoperative treatment of severe hyperthyroidism. *Surg., Gynec. & Obst.* 81:425-439, 1945.
2. McGinty, D. A., and Sharp, E. A. Effect of iodine intake on thyroid iodine distribution and thyroid weight of rats treated with thiouracil and other goitrogens. *J. Clin. Endocrinol.* 6:473, 1946.
3. Vander Laan, W. P., and Bissell, A. Effect of propylthiouracil and of potassium thiocyanate on uptake of iodine by thyroid gland of rat. *Endocrinology* 39:157-160, 1946.
4. DeRobertis, E. Personal communication.
5. Bartels, E. C. Propylthiouracil: its use in preoperative treatment of severe and complicated hyperthyroidism. *West. J. Surg.* (in press).
6. *Idem.* Thiouracil: remission or relapse of hyperthyroidism after discontinuing its use. *Am. J. Med.* 2:150-155, 1947.
7. Poate, H. R. G., and Spencer, S. L. "Thio" drugs in thyreotoxicosis. *M. J. Australia* 1:493-503, 1946.
8. Rawson, R. Personal communication.
9. Money, W., and Rawson, R. Experimental production of thyroid tumors in male rat. *Tr. Am. A. Study Goiter* (in press).

NEUROLOGIC DISTURBANCES WITH FOLIC ACID THERAPY*

PHILIP F. WAGLEY, M.D.†

BOSTON

THERE are numerous reports in the literature of the past two years on the excellent results obtained with folic acid in the treatment of pernicious anemia, sprue and nutritional macrocytic anemias. The observations presented below suggest some limitations of the therapeutic value of folic acid‡ and indicate that its use, in the present state of knowledge, for the treatment of pernicious anemia entails a definite risk.

Material and Observations

Fourteen cases of macrocytic anemia, 10 of pernicious anemia, 1 of tropical sprue, 2 of nontropical sprue, and 1 of macrocytic anemia associated with total gastrectomy were studied.

Pernicious Anemia

Cases 2, 3, 4, 7 and 10 occurred in patients with classic signs and symptoms of pernicious anemia who had initially shown excellent responses to the intramuscular use of refined liver extract. They had remained asymptomatic and without hematologic or neurologic relapse for several years on doses of 1 *U.S.P.* unit (injectable) a day given intramuscularly at intervals of four to six weeks. To determine the effect of folic acid, liver-extract therapy was stopped. The patients were then started on the folic acid regimens indicated in Table 1. As shown in the table, 3 patients (Cases 2, 3 and 4) had neurologic relapses with diminution in the vibratory sense in each. Two (Cases 2 and 3) were asymptomatic when the diminution of the vibratory sense was first demonstrable. However, 1 patient (Case 4) also complained of the appearance of numbness and tingling of the hands and feet associated with a sense of weakness; although no gross increase in papillary atrophy developed, the same patient began to complain of "burning" of the tongue. These relapses occurred from six to twelve months after folic acid therapy was started.

Two patients (Cases 7 and 10) have not shown neurologic relapses after nine and four months of therapy on 5 and 10 mg. of folic acid a day, respectively.

The following cases of pernicious anemia are presented in more detail because of individual variations.

CASE 1. A 40-year-old woman was admitted to the hospital with the chief complaint of weakness. The family and past histories were noncontributory. The present illness had begun approximately 2 years previously with transient sore tongue, easy fatigability and slowly progressive weakness. The pertinent physical findings were pallor, slight icterus, retinal hemorrhages, papillary atrophy of the tongue, a positive bilateral Babinski sign and slight diminution of the vibratory sense in the left leg. A serologic test for syphilis was negative. The red-cell count was 730,000, with a mean corpuscular volume of 134 cu. microns and a mean corpuscular hemoglobin concentration of 29 per cent. There was no free hydrochloric acid in the gastric secretions after the administration of histamine. Many megaloblasts were present in the sternal marrow. After being on 25 mg. of folic acid orally per day for 8 days the patient complained of sudden inability to void urine. Cystometric studies showed a toleration of 900 cc. of water without a voiding response. When once initiated the voiding response was well maintained. There was no residual urine. This was interpreted as indicating a sensory lesion. A marked progression in the loss of vibratory and position senses was evident at that time. The patient was immediately started on intramuscular liver-extract therapy. Seventy-six days later she was not anemic and had no difficulty in voiding. She continued to have

*From the Department of Medicine, Johns Hopkins Hospital and the Johns Hopkins University School of Medicine, Baltimore.

†Research fellow, American College of Physicians; research fellow, Thorndike Memorial Laboratory and assistant in medicine, Boston City Hospital; research fellow in medicine, Harvard Medical School; formerly, instructor in medicine, Johns Hopkins University School of Medicine, assistant resident physician, Johns Hopkins Hospital.

‡The folic acid employed in this work is synthetic pteroylglutamic acid and was supplied as Folvite through the courtesy of Dr. S. M. Hardy, of the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

slightly diminished vibratory sense over the left leg and a positive bilateral Babinski sign but was otherwise asymptomatic.

CASE 5. A 31-year-old Negress had been well maintained for several months on liver extract at the rate of 1 *U.S.P.* unit (injectable) a day given intramuscularly every 4 weeks. At the beginning of this study the patient was asymptomatic. She was taken off liver-extract therapy for a period of 4 months. At the end of that time she noted easy fatigability. Physical examination revealed no unusual conditions. Examination of the blood showed that the red-cell count had fallen to 3,200,000, with a mean corpuscular volume of 112 cu. microns and a mean corpuscular hemoglobin concentration of 31 per cent. The patient was started on 5 mg. of folic acid orally a day. At the end of 5 months of therapy she was asymptomatic. There was no papillary atrophy of the tongue. Neurologic examination was negative. Examination of the blood showed a red-cell count of 4,750,000. The mean corpuscular volume was 89 cu. microns, and the mean corpuscular hemoglobin concentration was 31 per cent. At the end of 7 months of therapy the patient complained of occasional sore tongue and numbness in the left leg. At the end of 10 months she complained of severe numbness and tingling in the arms, hands, legs and feet. The ankle jerks were of high threshold, with brief and sluggish response. The vibratory sense was diminished over the ankles, knees and iliac crests. The hematocrit remained at 44 per cent.

CASE 6. A 48-year-old Negress, who had been followed periodically for several years at the Johns Hopkins Hospital with the complaint of weakness, had responded well

TABLE 1. *Data in 14 Cases Treated with Folic Acid.*

CASE NO.	AGE	RACE	SEX	DIAGNOSIS	RED-CELL COUNT			MAXIMUM RETICULOCYTE COUNT	FOLIC ACID THERAPY		REMARKS
					INITIALLY	AFTER 2 WK.	ON LAST DAY		AMOUNT	ROUTE AND SCHEDULE	
	yr.				×10⁶	×10⁶	×10⁶	%	mg.		
1 (J. H. H. 411311)	40	W	F	Pernicious anemia	1.26	—	1.54	8.4	25	Orally, daily for 8 days	Vibratory sense diminished during therapy; difficulty in voiding.
2 (J. H. H. 227321)	73	W	F	Pernicious anemia	4.97	—	—*	—	10	Orally, daily for 12 mo.	By 12th mo. diminution of vibratory sense demonstrable at both ankles
3 (J. H. H. 240237)	42	W	F	Pernicious anemia	4.56	—	—*	—	10	Orally, daily for 11 mo.	By 11th mo. diminution of vibratory sense demonstrable at both ankles and both wrists
4 (J. H. H. 139407)	47	N	F	Pernicious anemia	4.17	—	—*	—	20	Orally, daily for 6 mo.	By 6th mo. numbness and tingling of hands and feet, with sense of weakness; vibratory sense in left leg diminished; burning sensation of tongue.
5 (J. H. H. 365004)	31	N	F	Pernicious anemia	3.20	—	4.75	—	5	Orally, daily for 10 mo.	By 10th mo. vibratory sense at ankles, knees and iliac crests diminished; sore tongue noted.
6 (J. H. H. 268067)	48	N	F	Pernicious anemia	1.41	2.85	4.20	15.4	30 10	Orally, daily for 27 days Orally, daily for 8 mo.	By 8th mo. numbness and tingling of hands and feet; unsteady gait; disappearance of abdominal reflexes and ankle jerks; marked diminution in tactile sensation; plantar responses not elicitable; urgency and dribbling of urine; relapse abrupt in onset and rapid in course.
7 (J. H. H. 159654)	50	W	M	Pernicious anemia	4.66	—	—*	—	5	Orally, daily for 9 mo.	After 9 mo. no symptoms or signs of relapse
8 (J. H. H. 377206)	56	W	M	Pernicious anemia	1.60	2.18	4.40	7.6	20	Orally, daily for 35 days	By 35th day numbness and tingling had appeared and progressed; severe soreness of tongue associated with glossal petechiae.
9 (J. H. H. 372244)	74	W	F	Pernicious anemia	1.10	3.10	4.80	42.0	100 15	Intravenously, daily for 26 days Orally, daily for 11 mo.	By 11th mo. progression of loss of vibratory sense, with numbness and tingling of hands and feet
10 (J. H. H. 194679)	60	W	M	Pernicious anemia	5.45	—	—*	—	10	Orally, daily for 4 mo.	After 4 mo. no symptoms or signs of relapse
11 (J. H. H. 391961)	70	W	F	Tropical sprue	2.64	3.60	3.70	9.2	45	Orally, daily for 20 days	After 20 days dramatic improvement; no neurologic disturbance.
12 (J. H. H. 286997)	65	W	M	Nontropical sprue	2.29	3.0	4.62	5.0	30	Orally, daily for 45 days	After 45 days moderate improvement; no neurologic disturbance.
13 (J. H. H. 130433)	43	W	M	Nontropical sprue	3.66	—	—*	1.2	100 45	Intravenously, daily for 5 wk. Orally, daily for 18 mo.	No definite improvement; no neurologic disturbance.
14 (J. H. H. 375636)	47	N	F	Pernicious anemia†	1.51	2.18	2.2	3.4	600 300	Intravenously, daily for 14 days Intravenously, daily for 2 days	Slight improvement with folic acid; slow but progressive improvement with liver extract.

*No significant change.
†This patient had undergone total gastrectomy

to liver extract intramuscularly at first, but after 3 years of infrequent attendance in the Outpatient Department she reappeared complaining of general weakness with numbness of the hands and feet. Physical examination showed marked pallor, slight papillary atrophy of the tongue and diminution of vibratory sense over the legs. A serologic test for syphilis was negative. Examination of the blood revealed a red-cell count of 1,410,000, with a mean corpuscular volume of 116 cu. microns and a mean corpuscular hemoglobin concentration of 34 per cent. Gastric secretion disclosed no free hydrochloric acid after the administration of histamine. The patient's blood responded dramatically to daily oral doses of 30 mg. of folic acid (Table 1). On the 28th day the daily dose was lowered to 10 mg. Six months after the beginning of treatment she was asymptomatic. Three months later, however, she returned complaining of abrupt onset of numbness and tingling in the hands and feet. She noted unsteadiness of gait and had some urgency and dribbling of urine. The tone of the adductor femoris muscles was increased. The abdominal reflexes and ankle jerks had disappeared. No plantar responses were elicited. Tactile sensation and appreciation of pinprick had markedly diminished over the legs.

Case 8. A 56-year-old machinist was admitted to the hospital with the complaint of a sore tongue and "feeling run down." The family and past histories were noncontributory. The present illness had begun 7 months prior to admission with anorexia, sore tongue and weakness. Physical examination showed pallor, injection and atrophy of the glossal papillae and normal neurologic signs. A serologic test for syphilis was negative. Examination of the blood disclosed a red-cell count of 1,600,000, with a mean corpuscular volume of 137 cu. microns and a mean corpuscular hemoglobin concentration of 31 per cent. There was no free hydrochloric acid in the gastric secretion after the administration of histamine. The sternal marrow showed numerous megaloblasts. The patient's blood revealed a good response to 20 mg. of folic acid a day orally (Table 1). However, after 35 days, numbness and tingling of the hands and feet appeared and progressed in severity. The soreness of the tongue became extremely annoying. Occasionally, the glossal surface showed tiny petechiae, and the papillae remained injected. The patient was started on liver extract intramuscularly. The soreness of the tongue, as well as the numbness and tingling of the hands and feet, disappeared by the end of 1 week.

Case 9. A 74-year-old housekeeper had first been admitted to the hospital in 1927 with pernicious anemia. For 1 year prior to the last admission in 1945 the patient had received no treatment. For several months she had noted increasing fatigability, dyspnea, slight ankle edema, a sore tongue and numbness and tingling of the hands and feet. Physical examination showed marked pallor, marked papillary atrophy of the tongue and diminution of the vibratory sense over both legs. A serologic test for syphilis was negative. Examination of the blood disclosed a red-cell count of 1,110,000, with a mean corpuscular volume of 135 cu. microns and a mean corpuscular hemoglobin concentration of 32 per cent. An occasional megaloblast was present in the peripheral blood. The patient was given intravenously 100 mg. of folic acid a day, prepared according to the technic described by Darby et al.[1] By the end of the 1st week she felt much stronger. On the 6th day of therapy a reticulocyte peak of 42 per cent was attained (Table 1). On the 26th day the patient was changed to daily oral doses of 15 mg. of folic acid. During the 10th month of such therapy numbness and tingling of the hands and feet recurred; the vibratory sense had disappeared below the costal margin and was diminished elsewhere.

Sprue

Case 11. A 70-year-old Porto Rican woman was admitted with the chief complaints of weakness, dizziness, vomiting and diarrhea. The patient's mother and sister had had a similar condition. The past history was noncontributory. Approximately 2½ years before admission loose, foul smelling, numerous bowel movements had begun. Weight loss and sore tongue were noted. Weakness became extreme. She was given "liver injections" by a physician and improved markedly. A few months prior to admission she neglected further therapy and relapsed. Physical examination showed emaciation, pallor, injected and atrophic glossal papillae and slight generalized abdominal tenderness. Neurologic examination was negative. A serologic test for syphilis was negative. Examination of the blood revealed a red-cell count of 2,640,000, with a mean corpuscular volume of 121 cu. microns and a mean corpuscular hemoglobin concentration of 33 per cent. The sternal marrow showed 7 per cent megaloblasts. The stools, which were pale, unformed, foul smelling and copious, contained no occult blood and showed no pathogenic ova or parasites. The oral glucose-tolerance and vitamin A absorption curves were flat.* X-ray studies of the gastrointestinal tract disclosed distortion of the mucosal pattern and pooling of the barium. The patient was placed on daily doses of 45 mg. of folic acid orally. By the 8th day the stools were much less frequent and were well formed. A reticulocyte peak of 9.2 per cent was attained on the 5th day of therapy. She became quite jovial and felt much stronger. Kymographic tracings of intestinal motility before treatment and 12 days after treatment showed changes indicating less frequent and less marked peristaltic waves. A glucose-tolerance test on the 17th day was normal. During the 3rd week of treatment the vitamin A absorption curve following the oral administration of 200,000 units remained quite flat, although the fasting serum vitamin A level had risen from 82 to 140 microgm. per 100 cc. during therapy. On the 20th day of therapy the patient was started on liver extract intramuscularly, since it was thought that she might neglect subsequent medical supervision and direction. She had developed no neurologic disturbances during folic acid therapy.

Case 12. A 65-year-old laborer with known nontropical sprue of 4 years' duration had responded well to the intramuscular use of liver extract. After 9 months of withdrawal of liver-extract therapy the patient was admitted with the chief complaints of recurrent episodes of diarrhea, weakness and numbness and tingling of the hands and feet. Physical examination showed evidence of recent weight loss, pallor and glossal papillary atrophy, with normal neurologic signs. A serologic test for syphilis was negative. Examination of the blood disclosed a red-cell count of 2,290,000, with a mean corpuscular volume of 125 cu. microns and a mean corpuscular hemoglobin concentration of 31 per cent. The two or three daily stools were well formed and had been for several days despite lack of medical therapy. The oral glucose-tolerance curve was flat, but the intravenous curve was normal. Folic acid was administered in doses of 30 mg. a day orally. On the 6th day of therapy a reticulocyte peak of 5 per cent was attained (Table 1). On the 21st day of therapy the vitamin A absorption curve remained flat (ranging from 38 to 54 microgm. per 100 cc. in the fasting and 3-hour serum specimens); on the following day the glucose-tolerance curve was normal. X-ray studies of the gastrointestinal tract 3 weeks after the institution of therapy continued to show alterations compatible with the clinical diagnosis of sprue. There were no episodes of diarrhea during a 45-day observation period. The patient gained 18 pounds in weight during that time, and the red-cell count rose to 4,620,000, with a mean corpuscular volume of 97 cu. microns. No neurologic disturbances developed during folic acid therapy.

Case 13. A 50-year-old man was followed medically over a period of 10 years with nontropical sprue. The family and past histories were noncontributory. During observation the patient had bulky, frothy, yellow, foul-smelling stools, from four to seven times or more daily, despite liver-extract given intramuscularly every 4 weeks at the rate of 1 *U.S.P.* unit (injectable) per day. Physical examination showed evidence of weight loss, pallor, no glossal papillary atrophy and a protuberant soft abdomen, with normal neurologic signs. A serologic test for syphilis was negative. Examination of the blood revealed a red-cell count of 3,660,000, with a mean corpuscular volume of 109 cu. microns and a mean corpuscular hemoglobin concentration of 31 per cent. The gastric secretion contained free acid. Folic acid in daily intravenous doses of 100 mg. was administered for 6 weeks. The bowel movements remained profuse, bulky and unformed. The oral glucose-tolerance curve remained flat, and administration of vitamin A orally in an amount of 200,000 units caused a level of only 25 microgm. per 100 cc. at the

*Vitamin A determinations were made by Dr. H. W. Josephs.

end of 3 hours. X-ray studies of the gastrointestinal tract continued to show hypermotility and changes compatible with the diagnosis of sprue. On 45 mg. of folic acid orally daily for 18 months the stools remained unformed and foul smelling and increased in number. The stool fat content remained high (42.5 per cent of the dry weight). The hematocrit did not rise. No abnormal neurologic signs or symptoms appeared.

Post-Gastrectomy Macrocytic Anemia

CASE 14. A 47-year-old Negress was admitted to the hospital with the chief complaint of inability to walk. The family history was noncontributory. The past history was of interest in that, 7 years prior to admission, the patient had been seen at another hospital complaining of abdominal cramps, anorexia and a 25-pound weight loss within a 6-month period. X-ray studies were interpreted as showing a gastric tumor mass. A total gastrectomy was performed. Microscopical sections of the gastric wall were subsequently studied by Dr. Arnold R. Rich and showed nonspecific lymphocytic infiltration. The patient remained asymptomatic and led a vigorous life until the present illness. Three months before admission the patient noted a rapid onset of numbness and tingling of the legs, associated with progressive inability to walk that became so severe 2 months later that she was confined to bed. There had been a 30-pound weight loss. Physical examination revealed evidence of recent weight loss, marked pallor and moderate papillary atrophy of the tongue. The tendon reflexes of the quadriceps femoris and semitendinosus were of very low threshold and showed brisk response. There was increased tone in the adductors of the legs and contractures of the gastrocnemius-soleus muscles. There was transient, partially sustained clonus on dorsiflexion of the left ankle. The Babinski signs were negative. The vibratory sense was absent below the iliac crests. Muscle strength was good. A serologic test for syphilis was positive. Examination of the blood revealed a red-cell count of 1,830,000, with a mean corpuscular volume of 128 cu. microns and a mean corpuscular hemoglobin concentration of 30 per cent. The sternal marrow showed 19.5 per cent megaloblasts. Direct visualization at the lower end of the esophagus demonstrated an esophagojejunal anastomosis and no gastric mucosa. The patient was given 300 mg. of folic acid intravenously daily for 2 days and 600 mg. intravenously daily for 14 days. The neurologic status was so serious that progression or improvement in such a short time could not be evaluated accurately. The red-cell count rose 600,000, and the hemoglobin rose 2 gm. per 100 cc. in 16 days. The reticulocyte count reached a peak of 3.2 per cent on the 8th day of therapy. On the 17th day folic acid was stopped and liver extract was given intramuscularly (10 *U.S.P.* units of crude extract and 15 *U.S.P.* units of refined extract) daily for several days, followed by an average daily dose of 1.5 *U.S.P.* units (injectable) of refined liver extract given every 2 to 4 weeks. There was no second reticulocyte peak. After 6 months the patient was able to walk easily without a cane. She had no numbness or tingling. The red-cell count was 5,200,000 6 months after the beginning of liver-extract treatment.

DISCUSSION

In the 10 cases of pernicious anemia treated with folic acid the patients who had anemia at the beginning of treatment showed very good hematologic responses. There was no hematologic relapse. Five patients had been asymptomatic while on liver-extract therapy for several years. However, 8 patients, while taking folic acid, showed neurologic disturbances of varying severity within periods ranging from eight days to twelve months. Two patients had difficulty with voiding of urine, 1 showing by cystometric study alterations suggesting a sensory lesion. Diminution in the vibratory sense and numbness and tingling in the hands and feet were the most frequent developments. One patient showed signs suggesting extensive damage to the reticulospinal tracts. Two patients, while still asymptomatic, gave evidence of progressive diminution of the vibratory sense in the lower extremity. The onset of signs and symptoms in 2 cases was abrupt and severe. Usually, the neurologic changes appeared clinically to be most marked in the sensory as contrasted to the motor modality. Three patients had either progression or return of soreness and burning of the tongue. In 1 case this was associated with gross changes consisting of papillary injection, atrophy and petechial hemorrhages. This patient responded within a week to liver extract given intramuscularly; at the end of that time there was no soreness and no glossal petechiae.

One patient with tropical sprue showed excellent clinical and hematologic response to folic acid therapy, but of 2 patients with nontropical sprue only 1 had a remission. The other, who had not previously responded to liver extract, showed no change in the blood either on parenteral or oral dosage and no marked change clinically. No neurologic disturbances developed in the cases of sprue during folic acid therapy.

A patient with total gastrectomy of seven years' duration, associated with macrocytic anemia, severe neurologic changes and weight loss, did not show a marked reticulocytosis or clinical improvement over a sixteen-day period of intensive folic acid therapy parenterally. There was a definite though small rise in the red-cell count and hemoglobin level. Although subsequent liver extract did not cause any rapid changes there was gradual and progressive improvement over a period of several months both hematologically and neurologically.

The high incidence of pathologic neurologic signs and symptoms developing among patients with pernicious anemia who previously had been adequately controlled with liver extract indicates the inadequacy of folic acid therapy for this aspect of the disease. That these disturbances did not follow doses of folic acid that were simply too small is indicated by other observations. Spies et al.[2] have stated that increasing dosages to amounts of 500 mg. a day have not ameliorated the progression of neurologic lesions in some cases. The abruptness and severity of neurologic relapse in an occasional case suggest the possibility of an actual deleterious effect of folic acid. In a series of 21 cases of pernicious anemia treated by Spies et al.[2] with doses of folic acid varying from 70 to 105 mg. a week, paresthesias and unsteady gait developed in 4. The dosage was then increased to 50 and even 500 mg. a day for ten to forty days without subjective or objective neurologic improvement. Nine other patients with subacute combined degeneration were then treated with folic acid. Two showed questionable improvement, whereas the remainder either became worse or did not improve. One patient revealed detectable progressive neurologic changes

after only twenty-two days of folic acid in daily oral doses of 10 mg.

Hall and Watkins[3] have reported 14 cases of pernicious anemia in relapse treated with folic acid. Of 10 patients with paresthesias of the extremities 8 improved. However, improvement was only temporary in 4, in whom paresthesias returned two to four months after the beginning of therapy. Two patients who had not had paresthesias prior to folic acid therapy developed them five months after the institution of treatment. Castle and Berk[4] have observed a neurologic relapse in 1 of 10 cases of pernicious anemia treated with folic acid. The less frequent incidence in their series may have resulted from the mode of administration. Their patients were given 75 mg. of folic acid intramuscularly at weekly intervals. Daily treatment was not given. Heinle and Welch[5] have observed an "explosive" and rapidly progressive neurologic relapse in a patient with pernicious anemia receiving folic acid therapy. Meyer[6] noted the development and progression of neurologic symptoms in 3 patients with pernicious anemia receiving folic acid in daily doses of 15 to 50 mg., orally, or 20 mg. intramuscularly.

The high incidence of glossitis during the treatment of patients with pernicious anemia is another symbol of the inadequacy of folic acid in their therapy. One patient's main complaint was severe glossal pain. Papillary petechiae developed during treatment. Although folic acid did not improve the condition, liver extract caused marked improvement in the discomfort and the petechiae disappeared within a week. Hall and Watkins[3] have reported that of 7 patients with pernicious anemia sustained improvement of the glossitis occurred in only 3.

The excellent response of tropical sprue to folic acid treatment seems well established.[7–9] However, in a case of nontropical sprue reported above no convincing improvement occurred with either folic acid or liver-extract therapy. The response of the other patient is difficult to evaluate, since he was in partial clinical remission when therapy was begun. He had previously responded well to liver-extract treatment Although so few observations warrant no definite conclusions, the differences in therapeutic effects in these 3 cases suggest that there are fundamental variants in the pathogenesis of sprue. Neurologic disturbances did not appear in any case of sprue during folic acid therapy.

Summary

The development or recurrence of neurologic disturbances occurred in 8 of 10 cases of pernicious anemia treated with folic acid. No hematologic relapse was observed.

The development or recurrence of neurologic disturbances was occasionally abrupt and severe, as well as rapid in course. The time of appearance could not be predicted.

In 3 of 10 cases of pernicious anemia glossitis either occurred during or did not respond to folic acid therapy.

One patient with tropical sprue responded dramatically. One patient with nontropical sprue responded very well, whereas another did not show any convincing improvement on folic acid or liver-extract therapy. Neurologic disturbances did not develop in the cases of sprue during folic acid therapy.

There was a slow effect of folic acid and liver extract in a patient with macrocytic anemia following total gastrectomy.

The observations presented indicate that the use of folic acid in the present state of knowledge entails a definite risk of injury to the nervous system in pernicious anemia.

References

1. Darby, W. J., Jones, E., and Johnson, H. C. Effect of synthetic Lactobacillus casei factor in treatment of sprue. *J. A. M. A.* **130**: 780-786, 1946.
2. Spies, T. D., and Stone, R. D. Liver extract, folic acid, and thymine in pernicious anaemia and subacute combined degeneration. *Lancet* **1**: 174-176, 1947.
3. Hall, B. E., and Watkins, C. H. Experience with pteroylglutamic synthetic folic) acid in treatment of pernicious anemia. *J. Lab. & Clin. Med.* **32**:622-634, 1947.
4. Castle, W. B., and Berk, L. Personal communication.
5. Heinle, R. W., and Welch, A. D. Folic acid in pernicious anemia: failure to prevent neurologic relapse. *J. A. M. A.* **133**:739-741, 1947.
6. Meyer, L. M. Folic acid in treatment of pernicious anemia. *Blood* **2**: 50-62, 1947.
7. Spies, T. D., et al. Effect of folic acid on sprue. *South. M. J.* **39**: 30-32, 1946.
8. Darby, W. J., Jones, E., and Johnson, H. C. Use of synthetic L. casei factor in treatment of sprue. *Science* **103**:108, 1946.
9. Spies, T. D., et al. Observations on treatment of tropical sprue with folic acid. *J. Lab. & Clin. Med.* **31**:227-241, 1946.

LIPEMIA RETINALIS*

Report of a Case

SAMUEL STEARNS, M.D.,† ELI FRIEDMAN, M.D.,‡ MAURICE LUGITCH, M.D.,§ AND SUMNER H. HOFFMAN, M.D.¶

BOSTON

LIPEMIA retinalis is a rare manifestation of the hyperlipemia that is commonly associated with diabetic acidosis. Since the original description by Heyl[1] in 1880, a total of 62 cases have been reported in diabetic and 6 in nondiabetic patients. The rarity of retinal lipemia is indicated by the experience of Joslin and his associates,[2] who discovered only 9 cases among 29,000 patients with glycosuria in a period of forty-eight years. However, the report of 7 patients with lipemia retinalis among 108 patients treated for diabetic acidosis at the Mayo Clinic[3] suggests that the condition is more frequent than was formerly believed.

The funduscopic picture of retinal lipemia is striking and pathognomonic. The vessels are flat, wide, ribbon-like and faint salmon to cream in color, with decreased or absent arteriolar reflex and with little or no distinction between arterioles and veins. The earliest changes are found at the periphery of the retina, advancing toward the disk during progression and receding with improvement. The changes, which may be transient, lasting only one or two days, usually do not disappear for a week, and may persist for even three weeks. Vision generally remains normal, despite the appearance of the retinal vessels. Three fourths of the reported cases have occurred among males and the majority of patients have been children or young adults, although the condition has been observed at the age of sixty-four years.[4]

The following case occurred in the youngest diabetic patient with lipemia retinalis on record.

CASE REPORT

A 4½-year-old girl was admitted to the hospital because of a 7-week history of increasing lassitude, polyphagia, polyuria, polydipsia and weight loss, culminating in drowsiness and in the discovery of sugar and acetone in the urine 12 hours before entry. Prior to the onset of this illness, the child had been of normal height and weight for her age. There was no family history of diabetes, and the past history was not relevant.

Physical examination revealed a thin, apathetic child who neither spoke nor responded to painful stimuli. She weighed 31½ pounds. There were no skin lesions. The pupils were equal and active, and the lenses clear. The fundi, which were pale, contained striking cream-colored ribbon-like vessels, which could not be differentiated into arterioles and veins. The disks were normal. The ears, nose and throat were normal except for a strong odor of acetone on the breath, dry mucous membranes and enlarged tonsils. There was no cervical adenopathy. The heart and lungs were normal. A firm liver edge could be felt one fingerbreadth below the right costal margin, but the abdomen was otherwise normal. Neurologic examination revealed only diminished deep tendon reflexes.

The temperature was 98.6°F. by rectum, the respirations 25, and the pulse 120; the blood pressure was 110/75.

Urinalysis disclosed a ++++ test for glucose and acetone, a ++ test for albuminuria and occasional leukocytes and epithelial cells in the sediment. Examination of the blood revealed a red-cell count of 4,150,000 and a white-cell count of 13,200; the smear was normal. When venous blood was placed in an oxalate bottle, the cells were noted to settle rapidly, leaving a creamy white supernatant plasma. Subsequent analysis disclosed a blood sugar of 256 mg. and a nonprotein nitrogen of 21 mg. per 100 cc. and a carbon dioxide combining power of 19 vol. per cent.

Immediately after entry, an intravenous infusion of physiologic saline solution was begun, and regular insulin was given subcutaneously at hourly intervals. By the end of the first 24 hours, the patient had received 300 units of insulin and 2900 cc. of saline solution of which 1300 cc. had also contained 5 per cent glucose. At that time the child was alert and responsive. The blood sugar was 85 mg. per 100 cc., the carbon dioxide combining power was 27 vol. per cent, and the urine was free of sugar and acetone. The blood cholesterol, which had not previously been determined, was 1010 mg. per 100 cc. The retinal vessels were slightly pinker but still paler than normal.

In the course of the following week, the diet was gradually increased, and the insulin dosage adjusted. On the 7th hospital day, the fundi were completely normal. On the 14th day, the blood cholesterol was 313 mg. per 100 cc. The liver was no longer palpable. X-ray examination of the skull and chest, a tuberculin test and urinalyses were all negative. The patient gradually gained weight and was discharged on the 23rd hospital day, when the fasting blood sugar was 94 mg. and the cholesterol 321 mg. per 100 cc. The 24-hour urinary glucose excretion was 14.5 gm. on a diet of 165 gm. of carbohydrate, 70 gm. of protein and 70 gm. of fat; 12 units of protamine-zinc insulin and 12 units of regular insulin injected separately constituted the daily morning insulin dosage.

DISCUSSION

Although quantitative fat determinations were not carried out, the cholesterol level of 1010 mg. per 100 cc., the creamy appearance of the plasma and the pathognomonic retinal picture established the diagnosis of lipemia retinalis in this case — the 63rd case and the youngest diabetic patient with this condition to be reported.

The rarity of such cases and the transitory nature of the retinal changes make it difficult to carry out experimental procedures that might result in an understanding of the pathogenesis of this condition. It is therefore worth while to summarize and correlate some of the observations that have already appeared in the literature.

Although lipemia retinalis has never been reported in the absence of hyperlipemia, a rise in blood fats does not in itself produce the condition. Uncon-

*From the Medical and Pediatric Services, Beth Israel Hospital.

†Assistant in medicine, Tufts College Medical School; associate in medicine, Beth Israel Hospital.

‡Associate professor of pediatrics, Boston University School of Medicine; head of pediatrics, Beth Israel Hospital.

§Associate in medicine, Beth Israel Hospital.

¶House officer in medicine, Beth Israel Hospital.

trolled diabetes and diabetic acidosis are frequently associated with hyperlipemia, but since 1880 only 62 cases of lipemia retinalis have been reported in diabetic patients. Furthermore, retinal lipemia has not been reported in conjunction with any of the numerous other conditions usually associated with hyperlipemia, such as starvation, asphyxia, phosphorus poisoning, pneumonia, nephritis, peritonitis and myxedema.

The conclusion that lipemia retinalis appears when blood lipids exceed 3.5 per cent and disappears when they decrease below 2.5 per cent[5] is not borne out by other observations. Persistence of retinal lipemia has been noted at a blood lipid level of 1.42 per cent,[6] and disappearance of the retinal changes has been reported during a rise in blood lipids from 9.15 to 10.8 per cent[7] and during a decrease from 21.7 to 16.3 per cent.[8]

Neither an elevated blood sugar nor the presence of diabetic acidosis is a necessary condition for the development of lipemia retinalis. A few cases of retinal lipemia have been reported in nondiabetic patients[9–14] in whom there was no evidence of acidosis. At least 2 of the diabetic patients with lipemia retinalis did not have simultaneous acidosis.[13, 15]

Attention has been called[16] to the observations of Boyd,[17] who found that milky serums sometimes contain normal amounts of fat whereas clear serums sometimes contain rather large amounts of fat. Visibility of the blood fats can be correlated with a relative decrease of phospholipids, so far as the total amount of natural fat, fatty acids, cholesterol and cholesterol esters is concerned.[17] Boyd concluded that phospholipids tend to maintain the other fat fractions in a supersaturated state in serum; when the phospholipid content of serum diminishes, lipids come out of solution as chylomicrons forming a milky emulsion. Such fat droplets have been demonstrated in lipemia retinalis in blood smears,[3] in capillary loops by the Lombard technic,[7] in muscle biopsy by frozen section and Sudan III stain[19] and in autopsy material.[20] The size of some of these droplets has been estimated as varying from that of a red cell to approximately 20 microns in diameter.[7] In normal serum, however, chylomicrons vary from 35 millimicrons to 1 micron in diameter.[21]

A relative decrease in phospholipids has indeed been observed in diabetic acidosis, in which Man and Peters[22] found that serum fatty acids rose much more than either the serum cholesterol or the phospholipids. In 2 cases of lipemia retinalis Marble and Smith[23] observed that the greatest increase in the blood fats had occurred in the fatty acid fraction, the next greatest in the cholesterol, and the least in the phospholipid fraction. A decrease in organic acid soluble phosphorus of the blood cells occurs with diabetic acidosis,[24] indicating a depletion of labile phosphorus reserves.[25] Significantly, although the blood chloride, sugar and carbon dioxide combining power promptly return to normal and phosphaturia promptly ceases with adequate treatment, the organic acid soluble phosphorus of the blood cells does not become normal for a week, at which time phosphaturia reappears.[25]

It seems probable, therefore, that depletion of phosphate reserves plays an important role in the pathogenesis of lipemia retinalis. A review of the literature reveals, in every completely reported case, a long preliminary period of uncontrolled diabetes, frequently with much weight loss and malnutrition. Although specific details are not presented in most cases of lipemia retinalis in nondiabetic patients, there is some reason to believe that the periodic vomiting, marasmus, alcoholic gastritis or hepatosplenomegaly variously reported in these cases had some bearing on the nutrition of the patients.

Summary and Conclusions

The 63rd and youngest patient with diabetic lipemia retinalis is reported. Lipemia retinalis is a retinal manifestation of hyperlipemia with a changed state of blood lipids in the direction of formation of larger than normal chylomicrons. Whatever the cause of the hyperlipemia, there is some evidence that the changed state of the blood fat results from depletion of phospholipids. This in turn may be due to a long period of malnutrition with, in diabetes mellitus, a specific loss of phosphates in the urine.

References

1. Heyl, A. G. Intra-ocular lipaemia. *Tr. Am. Ophth. Soc.* **3**:54-66, 1880.
2. Joslin, E. P., et al. *Treatment of Diabetes Mellitus.* Eighth edition. 783 pp. Philadelphia: Lea & Febiger, 1946.
3. Baker, T. W. Clinical survey of 108 consecutive cases of diabetic coma. *Arch. Int. Med.* **58**:373-406, 1936.
4. Falls, H. F. Lipemia retinalis: report of case. *Arch. Ophth.* **30**:358-361, 1943.
5. Parker, W. R., and Culler, A. M., Lipemia retinalis. *Am. J. Ophth.* **13**:573-584, 1930.
6. Chase, L. A. Diabetic lipemia retinalis: report of case. *J. A. M. A.* **97**:171, 1931.
7. McCann, W. S. Lipemia retinalis. *Bull. Johns Hopkins Hosp.* **34**: 302-304, 1923.
8. Jafee, M., and Schonfeld, W. A. Lipemia retinalis due to diabetes mellitus, with report of case. *Arch. Ophth.* **9**:531-537, 1933.
9. Wagener, H. P. Lipemia retinalis: reports of three cases. *Am. J. Ophth.* **5**:521-525, 1922.
10. Holt, L. E., Jr., Aylward, F. X., and Timbres, H. G. Idiopathic familial lipemia. *Bull. Johns Hopkins Hosp.* **64**:279-314, 1939.
11. Goodman, M., Shuman, H., and Goodman, S. Idiopathic lipemia with secondary xanthomatosis, hepatosplenomegaly and lipemic retinalis. *J. Pediat.* **16**:596-606, 1940.
12. Chapman, F. D., and Kinney, T. D. Hyperlipemia: "idiopathic lipemias." *Am. J. Dis. Child.* **62**:1014-1024, 1941.
13. Kaufman, M. L. Lipaemia retinalis. *Am. J. Ophth.* **26**:1205-1208, 1943.
14. Lepard, C. W. Lipemia retinalis in nondiabetic patient. *Arch. Ophth.* **32**:37, 1944.
15. Igersheimer, J. Retinal lipemia and visual disturbances associated with acromegaly and diabetes mellitus: report of case. *New Eng. J. Med.* **226**:754-757, 1942.
16. McKee, S. H., Wilson, D. R., Fowler, A. F., and Wilen, B. Lipemia retinalis. *Am. J. Ophth.* **25**:513-521, 1942.
17. Boyd, E. M. Lipid composition of "milky" blood serum. *Tr. Roy. Soc. Canada* **31**:11-16, 1937.
18. Ferber, J., and Apperman, I. Lipemia retinalis diabetica. *M. J. & Rec.* **125**:815-817, 1927.
19. Allen, J. H., and Howard, W. A. Lipemia retinalis: report of case. *Am. J. Ophth.* **19**:645-648, 1936.
20. Starr, L. Lipaemia and fat embolism in diabetes mellitus. *Med. Rec.* **17**:477-481, 1880.
21. Frazer, A. C. Fat absorption and its relationship to fat metabolism. *Physiol. Rev.* **20**:561-581, 1940.
22. Man, E. B., and Peters, J. B. Lipoids of serum in diabetic acidosis. *J. Clin. Investigation* **13**:237-261, 1934.
23. Marble, A., and Smith, R. M. Blood lipids in lipaemia retinalis. *Arch. Ophth.* **15**:86-94, 1936.
24. Guest, G. M., and Rapoport, S. Acid-soluble phosphorus compounds of red blood cells in diabetic acidosis. *Am. J. Dis. Child.* **60**:450, 1940.
25. Guest, G. M., and Rapoport, S. Organic acid-soluble phosphorus compounds of blood. *Physiol. Rev.* **21**:410-437, 1941.

MEDICAL PROGRESS

THE TOXEMIAS OF PREGNANCY

BENJAMIN TENNEY, JR., M.D.*

BOSTON

THIS review of the toxemias of pregnancy considers the four syndromes involving primarily hypertension with or without albumin in the urine. The first two are essential hypertension and renal disease; they may or may not be influenced by pregnancy. Secondly, pre-eclamptic toxemia and eclampsia are discussed. These conditions are the result of the pregnancy itself. It should be stated in the beginning that clinical diagnosis and classification are frequently difficult and often impossible. If a patient is first seen after she has become pregnant, the presence of hypertension or albuminuria or both offers a very confused picture. There are many leads suggesting the fundamental disease, which may or may not be present, but, in many cases, the final diagnosis cannot be confirmed until months after the patient has been delivered. Even then, there may be doubt regarding the actual condition involved.

It is also extremely important to realize that in all cases in which there is basic renal or vascular disease, true toxemia of pregnancy may be superimposed on the original condition. In fact, any pregnant woman who has had renal or vascular disease previous to pregnancy has a much greater chance of developing true toxemia than one with a healthy renal vascular system. For instance, a woman with chronic nephritis may become extremely ill in pregnancy from the chronic nephritis, but she may become more acutely and rapidly ill from the development of a superimposed pre-eclamptic toxemia. Frequently, it is extremely difficult to recognize when a previous renal vascular disease develops into pre-eclamptic toxemia. Fortunately the treatment is in a large degree essentially the same, but the prognosis and the speed with which dangerous symptoms develop vary in the different conditions. A woman with chronic nephritis can carry a much greater hypertension with reasonable safety than one with a true pre-eclamptic toxemia. A patient with essential hypertension may go through pregnancy uneventfully with a hypertension that in a pre-eclamptic might suddenly develop into eclampsia. Therefore, the best clinical judgment and all available laboratory facilities must be used to distinguish between the different entities. Dexter and Weiss[1] emphasize the importance of the distinction in the following statement: "Organs weakened by pre-existing hypertensive disease are more susceptible to the strain imposed upon them by toxemia than are organs previously healthy, there being a greater tendency to cardiac decompensation, renal insufficiency, and more severe retinal lesions."

*Associate professor of obstetrics, Boston University School of Medicine; assistant visiting surgeon in obstetrics and gynecology, Boston City Hospital; assistant obstetrician, Massachusetts General Hospital.

ESSENTIAL HYPERTENSION

Essential hypertension in pregnancy is a hypertension that existed previous to pregnancy. There are cases in which, although no hypertension has been recorded before pregnancy, the disease or tendency exists and shows up early in pregnancy. It is reasonable to state that any hypertension developing in the first half of pregnancy is not pre-eclamptic toxemia. Without any signs of permanent kidney damage, this rise in blood pressure is presumably due to essential hypertension. If a patient develops a blood pressure of 140 systolic, 90 diastolic, before or during the first half of pregnancy, without signs of kidney damage, the case must be classed as essential hypertension. In this hypertension the systolic pressure frequently rises to 180. In mild cases there is little else to show, and the patient feels well. There is usually no albumin in the urine. These patients will generally do well. They must be watched more carefully than the normal patient, and they must be more careful of their diet and activities, owing to the greater danger of developing toxemia.

The etiology of essential hypertension is unknown, as is that of pre-eclamptic toxemia. The similarity of the two conditions is marked, since in both cases, the primary hypertension is due to spasm of the arterioles. In essential hypertension the long-continued progress of the disease causes hypertrophy of the arteriolar muscle and finally degeneration of that muscle with fibrous displacement. The duration of pre-eclamptic toxemia is sufficiently limited so that this final permanent damage to the arterioles does not take place. However, if the toxemia is allowed to continue too long, permanent damage to the arterioles takes place. In the benign type of hypertension, permanent kidney damage is a late complication. In the malignant type, renal insufficiency develops early, and this is the chief danger. There is probably a marked hereditary tendency in essential hypertension. Certain people have a marked constitutional abnormality, which may lead to the

development of hypertension. The cold pressor test is of interest, in that the great majority of essential hypertensive patients give positive reactions. Also, a large number of otherwise normal people who react to this test will eventually develop hypertension.

The work of Grollman[2] in essential hypertension suggests a relation to pre-eclamptic toxemia. He states that the kidney — by some humoral, if not by an incretory, mechanism — may be concerned in the pathogenesis of hypertensive cardiovascular disease as commonly observed in man, and as produced with ease in the experimental animal. The fact that hypertension follows manipulations of the kidney, as well as the high incidence of hypertension observed in the human being with kidney disease, leaves little doubt that the experimental disease, as well as many cases of clinical hypertension, is secondary to dysfunction of the kidney.

According to Grollman[2] the removal of the injured kidney, either in man or in animals, does not lower the blood pressure. If one kidney is injured and the other is removed, there is an immediate rise in the pressure. In contrast to much previous work, he believes that the normal kidney produces an incretory substance that regulates the normal blood pressure, and that the removal of normal kidney tissue, or damage to it, removes this control over blood pressure and thus results in hypertension.

The work of Smithwick[3] in lumbodorsal sympathectomy throws an interesting light on the relation of essential hypertension to pre-eclamptic toxemia. The marked lowering of hypertension following this operation frequently allows patients to proceed uneventfully through pregnancy. These patients, with the hypertension previous to operation, would be serious risks for pregnancy. One patient in particular, who with a previous pregnancy developed severe cerebral and visual disturbances, had to have the pregnancy terminated at seven months. After a sympathectomy, she went uneventfully through a normal full-term pregnancy. In spite of this operation some of these patients develop pre-eclamptic toxemia. In a series of 13 cases reported by Newell and Smithwick,[4] 3 patients developed definite signs of pre-eclamptic toxemia; 1 had a premature separation of the placenta, and in 1, labor had to be induced before term.

The prognosis of essential hypertension of the benign type in pregnancy is good. The majority of these patients have an uneventful pregnancy. The incidence of pre-eclamptic toxemia is higher in them than in normal women, and they should be watched more carefully. Particularly, they should have sufficient rest, a careful diet and a minimum weight gain. Any increase in hypertension, or the appearance of albumin in the urine, indicates the probability of the development of pre-eclamptic toxemia. Dexter and Weiss[1] believe that women with prepregnant hypertension (essential hypertension) pass through pregnancy without damage if they do not develop pre-eclamptic toxemia. They consider an added risk to the fetus to exist in these cases. Sharkey and Hess[5] state that pregnancy causes no significant change in essential hypertension. They do not regard the hypertension as having any effect on the infant. In their own series, these patients did as well as the normal women.

In a series of 301 pregnant patients, Chesley, Annitto and Jarvis[6] report 218 cases classifiable as hypertensive toxemia. The outstanding hazard of pregnancy is the superimposition of toxemia, which occurred in about 30 per cent. The incidence of eclampsia in these hypertensive patients was ten times that in all patients, whereas the incidence of pre-eclampsia increased seven times. The gross fetal mortality was 34 per cent. The majority of hypertensive women apparently are not jeopardized by pregnancy: two thirds of these patients escaped superimposed toxemia. In patients who did not have toxemia, 30 per cent had greater hypertension at follow-up study than when originally observed. The authors conclude that repeated pregnancies are not harmful to the hypertensive woman. The pregnancy itself is hazardous should toxemia occur. If the toxemia causes damage, the prompt interruption of a hypertensive pregnancy, at the first sign of developing toxemia, should benefit the patient.

Essential hypertension of the malignant type is a more serious disease. Without pregnancy, the prognosis of these patients is poor. The added strain of pregnancy is apt to precipitate serious complications. Pregnancy should be definitely avoided in such cases.

Renal Disease

The differentiation of the various forms of kidney disease is somewhat of an academic problem. The separate types — glomerular, arteriosclerotic, nephritic and pyelonephritic — offer great difficulty in differential diagnosis. It is vital that the clinician recognize permanent kidney disease. All types of kidney disease are alike, in that they respond poorly to pregnancy. Any damaged kidney has a lowered reserve. The additional load of pregnancy may be too much for this lack of reserve. Pregnancy may cause renal failure. Patients with damaged kidneys may develop a superimposed pre-eclamptic toxemia. The incidence of toxemia in these patients is much higher than that in normal persons. It is often extremely difficult to judge when a nephritis may show renal failure in pregnancy, but the addition of toxemia will make the condition more acute and rapid in progress. It is also essential to realize that patients may have renal disease from childhood infections, or other causes, of which they are entirely unaware. Often, it is the first pregnancy that brings the kidney disease to light. A negative past history obtained from a patient does not rule out the possibility of renal damage.

The symptoms of renal disease appear early in pregnancy. The milder forms may not appear until later. It is the mild forms that are most frequently confused with pre-eclamptic toxemia. A patient who appears during the first months of pregnancy with hypertension, albuminuria and edema should be studied for the presence of nephritis. The systolic blood pressure is variable, sometimes being over 200; usually it is lower. Extremely high blood pressures with no cerebral symptoms are characteristic of chronic nephritis rather than pre-eclampsia. The urine will show albumin, and frequently casts and red cells, in contrast to pre-eclampsia. The blood pressure does not fall immediately after delivery as in pre-eclampsia but continues for months and often permanently. The albumin may persist after delivery. Nitrogen retention may be present in the severe cases as shown by a high blood nonprotein nitrogen. In pre-eclampsia there is no nitrogen retention. According to Stander[7] a high nonprotein nitrogen is pathognomonic of kidney disease. This is not found in pre-eclampsia unless eclampsia develops. According to Stander a study of the renal-function tests is essential. In pre-eclampsia the kidney function is normal, whereas in kidney disease a decreased function is often found. Stander recommends the fifteen-minute phenolsulfonephthalein, the urea clearance and the dilution and concentration tests. He believes that the dilution and concentration test is the most sensitive to slight degrees of kidney damage. Examination of the eye grounds frequently shows the presence of retinal hemorrhage and albuminuric retinitis, which is absent in pre-eclampsia.

The prognosis of renal disease in pregnancy is poor. Stander gives the average maternal mortality occurring within ten years, after the disease has been recognized, as 40 per cent. Each pregnancy increases the kidney damage and undoubtedly shortens the life of the patient. The prognosis for the babies is extremely poor. DeLee[8] gives the fetal mortality as 66 per cent. Many women with renal disease abort. In many others the infant dies during labor and delivery. Commonly the babies die in utero during the last month of pregnancy. The prognosis for the fetus is so poor that induction of labor when the fetus is viable is frequently the best procedure. The large placental infarcts that are often found in chronic nephritis, involving from one quarter to one half of the placenta, threaten the life of the fetus during the later months and during labor itself. Premature separation of the placenta occurs in chronic nephritis, although not so commonly as in the pre-eclamptic toxemias.

A woman with proved renal disease should not become pregnant. Her chances of obtaining a living healthy baby are about one in three. The pregnancy will shorten her life, owing to increased kidney damage. There is also the risk of the pregnancy itself with the large incidence of pre-eclamptic toxemia, as well as other accidents of pregnancy, which these patients do not stand well. Should a patient be seen when she is already pregnant and the renal damage is slight, an attempt may be made to carry her through the pregnancy. The dangers should be explained to her and her husband. She should be carefully watched, given a proper diet and liquid intake, and sufficient rest, and immediately hospitalized if any sign of renal failure appears. In the severe cases, the prognosis for the baby is so poor, and the danger to the mother so great, that abortion should be performed immediately.

Pre-Eclamptic Toxemia

The following definition by Dexter and Weiss[1] is as specific a description of this condition as can be made:

> Toxemia of pregnancy (pre-eclampsia and eclampsia) is a humoral and vascular disorder characterized by the appearance, in the second half of pregnancy, of an excess of edema, an elevation of the blood pressure or an increase in the amount of albumin in the urine, or both, above that present before or in the early weeks of pregnancy, and a rapid decrease of edema, lowering of blood pressure, and of the amount of albumin in the urine soon after delivery.

These authors continue with the following statements. Toxemia of pregnancy differs from nonpregnant hypertension chiefly in its relation to water retention. The hypertension of early toxemia is not of renal origin. The toxemia syndrome occurs in mothers with pre-pregnant hypertensive disease as well as in those without. The two most important predisposing factors to development of toxemia are pre-pregnant hypertension (in one third of the cases) and generalized edema (in 85 per cent).

According to Dieckmann[9] the development of pre-eclamptic toxemia is influenced by diet, habits and climate. A hot, wet climate is most favorable for the development of eclampsia. He states that the Mohammedans in India develop more eclampsia than the Hindus or Christians owing to the difference in the amount of meat in the diet. The elimination of sodium chloride, proteins and fats lowers the incidence of severe pre-eclampsia and eclampsia, but not of mild pre-eclampsia.

Eastman[10] gives the statistics of 2418 pre-eclamptic patients over a period of twenty years. In this series there were 92 cases of eclampsia, or an incidence of 3.8 per cent. In eclampsia the maternal mortality was 7.6 per cent, and the fetal mortality 21.7 per cent. The maternal mortality in pre-eclampsia was 0.2 per cent, and the fetal mortality was 6.8 per cent. In twenty years the incidence of eclampsia resulting from pre-eclampsia was reduced from 14.2 to 2.3 per cent. This reduction was due to the earlier recognition of pre-eclampsia and better treatment of that condition.

Cosgrove and Chesley[11] report a series of 1625 cases of pre-eclamptic toxemia. The maternal mortality in this series was 1 per cent. The inci-

dence of premature separation of the placenta was 3.8 per cent, and that of eclampsia was 5.5 per cent. The total fetal mortality was 17.1 per cent. The authors state that prophylaxis cannot prevent the actual occurrence of toxemia.

The first appearance of hypertension or albuminuria or both with a sudden gain in weight in the last trimester in pregnancy must be taken to mean the development of pre-eclamptic toxemia. If there is a sudden gain in weight, without the development of hypertension or albuminuria, the possibility of impending toxemia must be considered. A sudden gain in weight in a woman who has been on a reasonable diet usually indicates the presence of visible or invisible edema or of fluid retention.

Dexter and Weiss[1] found generalized edema in 64 per cent of otherwise normal pregnant women. The physical characteristics, distribution, etiology, time of appearance and post-partum disappearance were identical with those of women with toxemia. In 100 patients with edema, the history of previous menstrual headaches and premenstrual edema was twice as frequent as that in patients without edema. Frequently, the appearance of generalized edema was followed shortly by the appearance of toxemia. The incidence of toxemia in women with generalized edema was far greater than that in those without. They were unable to explain the presence of edema by hydrostatic pressure, increased capillary permeability, hypoproteinemia or anemia. A humoral etiology was suspected.

Dieckmann[9] explains the formation of edema by: decreased colloid osmotic pressure of serum proteins; increased permeability of capillary walls; and increased capillary pressure. The venous pressure in the leg veins is increased in normal pregnancy, causing a retardation in the absorption of fluid. The capillaries are more permeable. There is a delayed excretion of water and sodium chloride. Edema of the ankles in pregnancy is normal, but other edema is not. Hidden edema is best shown by weight gain, and is often the earliest symptom of toxemia. There is a rapid increase of the incidence of toxemia in excessive weight gain.

The appearance of edema in otherwise normal pregnant women is such a common occurrence that it is frequently not regarded with sufficient gravity. The increased incidence of toxemia following fluid retention is well known. Edema can be partially controlled and sometimes eliminated by proper diet and fluid intake. The fluid intake of any woman developing edema should be restricted. A pregnant woman can be comfortable on as little as 1 liter of fluid in twenty-four hours. The relation of sodium intake to fluid retention is important. It has been shown that the elimination of sodium from the diet often lowers the blood pressure. If salt and sodium compounds are removed from the diet and fluids are limited, most women will excrete a large amount of the retained fluid and lose a corresponding amount of weight.

Hypertension in pre-eclamptic toxemia (a blood pressure above 140 systolic, 90 diastolic) appears before albumin in the urine in the majority of cases. Hypertension or albuminuria, or both, does not appear before the last trimester of pregnancy. A pregnant woman who has passed uneventfully through the first six months of pregnancy and then develops hypertension presumably has pre-eclamptic toxemia. The blood pressure in this disease runs at a lower level than that in chronic nephritis and essential hypertension. A systolic pressure of 160 in toxemia is a dangerous level. Eclampsia develops at this and at slightly higher levels. This hypertension is due to arteriolar spasm and is not the result of primary kidney disease. This is true only from a clinical standpoint, for it is possible that kidney damage could be demonstrated by more sensitive kidney-function tests than are now available. The level of hypertension must be watched very closely. A steady and rapid rise in blood pressure, even though not great in extent, is an indication of the severe or fulminating type of toxemia, in which eclampsia rapidly develops. In the milder forms of pre-eclampsia, the blood pressure rises slowly and will hold a given level for weeks, or even fall, under the proper medical treatment. When the blood pressure continues to rise in spite of medical treatment the pregnancy should be terminated.

In pre-eclampsia, albumin is the only abnormal finding in the urine. The albumin may appear at first as a very slight trace or may appear rapidly in large amounts. The amount of albumin present has some relation to the severity of the disease but is not so accurate a guide as the hypertension. The small number of cases in which albumin appears first are of the milder form. The presence of casts or blood cells suggests kidney disease rather than true toxemia. In the fulminating type of pre-eclamptic toxemia and in eclampsia, blood cells and casts may appear, owing to secondary damage to the kidney from the toxemic process.

As pre-eclampsia progresses, further symptoms are likely to develop. These symptoms usually indicate a more serious and advanced stage of the disease. The cerebral symptoms most often start with headache, which may develop further into dizziness and drowsiness. Visual symptoms, such as diplopia, scotoma and blurred vision, are of serious prognosis. Nausea and vomiting with epigastric pain may be the precursor of eclampsia. When pre-eclampsia is recognized in its earliest stages and responds to proper treatment, these symptoms should not develop; their appearance indicates that the disease is progressing unfavorably.

The etiology of pre-eclampsia is unknown, in spite of much study and investigation. There are many predisposing factors and some fundamental findings

in this disease. Dexter and Weiss,[1] who state that there is some evidence that toxemic patients are more sensitive to the effect of posterior pituitary substance than others, were unable to cause permanent hypertension in rabbits with large and repeated doses of posterior pituitary extract. There were no significant histologic changes in these rabbits. Extracts of placentas from patients with high blood pressure were injected into rabbits without causing any pressor effects, and no such effects were obtained with amniotic fluid. Renin could not be demonstrated in the placentas of patients with increased blood pressure. There was no rise in blood pressure in babies delivered of toxemic mothers. It was concluded that if a pressor substance is present in the mother, it does not cross the placenta. In 16 cases with death of the fetus in utero, 11 mothers showed no improvement of the toxemia until after delivery. These cases indicate that the placenta was the important factor in toxemia.

Dieckmann[9] states that Pituitrin causes a marked rise in blood pressure and suppression of urine in pre-eclampsia. This effect was not observed in hypertensive and renal disease. The thyroid gland is enlarged in the majority of pregnant women. A deficiency in thyroid causes an increase in tissue fluids that contain more proteins. The retention of extracellular fluid may be tremendous. Hypothyroidism produces hypercholesteremia in rabbits, with severe endarteritis of the placental arteries. Colvin and Bartholomew[12] found no cases of toxemia in patients in early pregnancy with a basal metabolic rate of +10 per cent or above. There was an increasing incidence of toxemia as the basal metabolic rate fell. In patients with a rate of −10 per cent or below, there was an incidence of 50 per cent. Many believe that thyroid extract is a good prophylactic against pre-eclampsia.

Smith and Smith[13] have found high levels of chorionic gonadotropin and low estrogenic activity in the blood and urine of toxemic patients. There is also a deficiency of progesterone; the same titer occurs normally just before and during labor. This hormone change occurred weeks before the development of toxemia. The authors believe that fortnightly measurement of the serum gonadotropic hormone, from the fifth month on, will reveal an abnormal rise, eight to ten weeks before the disease becomes clinically apparent, in about 80 per cent of cases. Premature deterioration of placental steroids may be prevented by large doses of diethylstilbestrol. Large doses of estrogenic substance will also increase the production of progesterone. Sufficient clinical work has not been done fully to evaluate this treatment for pre-eclamptic toxemia. Large doses of estrogenic substance after the signs of toxemia have appeared have proved of little value. If a sufficient number of cases were studied and treated early in pregnancy, before the onset of toxemia, the results could be correlated against the incidence of toxemia in a control group.

More recently Smith[14] has become interested in a toxin isolated from normal menstrual blood. He is impressed by the resemblance of certain physiologic findings in menstruation and toxemia. He mentions retention of water, the decrease of serum diastase, the increased uterine irritability, the systemic disease, which he states is like that of premenstrual and early menstruating endometrium, and, finally, the amelioration of the disease when the uterus is emptied and the removal of the decidua is under way. He has been unable to demonstrate the presence of menstrual toxin in pre-eclampsia or eclampsia. A protective pseudoglobulin has been developed for the treatment of pre-eclamptic toxemia. There was a fall in the blood pressure, as well as a decline in the amount of albumin in the urine, in the patients treated. This work is of great interest because, in many ways, the toxin has the properties necessary for toxemia. However, this toxin has not as yet produced toxemia in animals or human beings, and the clinical results of treatment are still too few and indefinite for any final conclusions.

Cosgrove and Chesley[15] state that definite functional and structural changes in the vascular system, particularly the capillaries and arterioles, are the most universal pathologic tendency in pre-eclampsia. Hertig[16] remarks that toxemia of pregnancy — in all its manifestations, including eclampsia, toxic separation, cortical necrosis, pituitary necrosis and placental degenerations — is part of the same fundamental process. A pathological classification of the separation of the normally implanted placenta fixes the blame for the mortality in this condition, almost, if not wholly, on the toxic variety. Certain placental degeneration that occasionally occurs in all the groups of the American classification, including so-called "minimal toxemia," may cause the death of the fetus in utero. He stresses the fact that some babies due to die in utero from this cause may be saved by prompt action when fetal growth has ceased. The smaller the infant, the more certain it is that placental degeneration exists.

Tenney and Parker,[17, 18] in a study of the histopathology of the placenta in pre-eclamptic toxemia and eclampsia, found a placental lesion characteristic of this disease. The lesion consists primarily of a premature aging of the placenta, which takes place in the syncytium of the small villus buds. A normal full-term placenta will show from 10 to 50 per cent degenerated buds. A count of one hundred to two hundred villus buds should be made for an accurate determination. In pre-eclampsia and eclampsia this degeneration involves from 50 to 100 per cent of the syncytial buds. It is extremely important that the actual age of the placenta be taken into account. Syncytial degeneration in the normal placenta does not begin before the eighth month and, as stated

above, does not reach over 50 per cent at term. Therefore, in a seven-month placenta, there should normally be no syncytial degeneration. The finding of a moderate amount (about 25 per cent) of syncytial degeneration in a seven-month placenta would be indicative of pre-eclamptic toxemia, whereas in a full-term placenta, there would have to be over 50 per cent to indicate toxemia. In essential hypertension, uncomplicated by toxemia and renal disease, this typical degeneration is not found. The amount of syncytial degeneration observed in toxemia is relative to the severity of the disease. In 100 cases of pre-eclamptic toxemia, pronounced placental lesions were noted in 60 per cent. In 90 per cent of these cases albuminuria was present. In the other 40 per cent, which showed less pronounced lesions, albuminuria was present in less than half. This suggests that placental damage begins before clinical symptoms appear. If the syncytium is regarded as similar in function to the glomerular epithelium of the kidney, the destruction of this epithelium, together with circulatory congestion, may explain the high fetal mortality in this condition.

The renal changes in toxemia are best described by Bell.[19] The glomeruli are slightly enlarged. The lumens of their capillaries are narrowed, and sometimes completely closed, so that they contain but few erythrocytes. The decrease of the capillary lumens is caused mainly by thickening of the capillary basement membrane. The increase in the endothelial cells is variable. Dexter and Weiss,[1] in a study of 25 cases of fatal eclampsia that came to autopsy, found the combination of microscopical changes observed in the kidneys specific and characteristic for toxemia in all cases. The lesions were primarily degenerative, and the term "glomerulonephrosis" seemed most suitable. These changes are sometimes noted in mild pre-eclampsia.

The typical liver lesion of eclampsia was found in only 50 per cent of autopsies at the Mallory Institute of Pathology. This lesion consists of hemorrhagic necrosis of the peripheral portion of the liver lobules. When this lesion is found, it is definitely specific for eclampsia. In this connection the work of Ingerslev and Teilum[20] is of interest. They performed aspiration biopsies on the livers of normal pregnant women and on those with pre-eclamptic toxemia and eclampsia. There were no changes in the livers of the former and no histologic or chemical grounds to maintain the concept of a pregnancy liver. In pre-eclampsia the authors also found no change. In eclampsia peripheral hemorrhagic necrosis was observed in 50 per cent of cases. The liver damage in the patients with toxemia appears to have been a terminal result, not a cause, of severe disease.

Dieckmann[9] describes extensive cerebral hemorrhage in 15 to 20 per cent of autopsies in deaths from eclampsia.

The physiochemical changes in the blood and urine of women with pre-eclamptic toxemia have been thoroughly studied by many investigators. Unfortunately, there is no physiochemical test that is pathognomonic of this disease. The nonprotein nitrogen of the blood is not high in pre-eclampsia. It is only in the later stages and in eclampsia that a rise is found. Stander[7] describes a high blood uric acid which is an important aid in the differentiation of pre-eclamptic toxemia, but it is not a consistent finding. Dieckmann[9] describes a blood concentration in severe pre-eclampsia and eclampsia, but this is not found in the mild cases.

Eastman[10] gives four objectives in the treatment of pre-eclamptic toxemia: prevention of convulsions; prevention of residual hypertension; delivery with minimal trauma and yet in a manner that will not handicap the patient in future pregnancies; and delivery of a living child.

Prophylaxis is the first and most important treatment. Every pregnant woman should be under medical care from the time that she first knows she is pregnant. She should be on a high-protein diet including plenty of meat, fish, eggs and milk. She should have a low-fat and low-carbohydrate intake. Salt and other sodium compounds should be limited to a minimum. Fluids should be allowed in amounts necessary for comfort, but excessive fluid intake should be avoided. The weight should be carefully followed; the weight gain for the entire pregnancy should be limited to 20 pounds. If the patient becomes overweight, she should try to reduce. In cases of excessive weight gain, the patients should be put on a diet of 1200 calories. If the patient does not co-operate and obtain an immediate weight loss, she should be hospitalized, and the weight reduced under supervision. She should be given iron and vitamins during the entire pregnancy and should have sufficient rest and a moderate amount of exercise. Proper and regular bowel elimination is important.

If hypertension or albuminuria, or both, develops in the last trimester of pregnancy, the patient should first be treated by medical means. She should be confined to bed and put on a high-protein, fat-free diet. All salt and sodium must be eliminated from the diet. If there is visible edema or an increase in weight, 1 liter of fluid daily should be prescribed, and one good cathartic and sufficient laxative for a daily bowel movement should be given. A sedative is helpful. Frequently, a patient improves and can be up and about on a restricted regime.

If the patient does not respond to the treatment outlined above she must be hospitalized. The same regime is continued under hospital care, with the possible addition of intravenous hypertonic glucose. Blood-pressure readings must be taken frequently, a careful record kept of the fluid intake and output, and daily catheterized specimens exam-

ined in the laboratory. If, in spite of treatment, the blood pressure continues to rise and the albuminuria increases, termination of the pregnancy is indicated.

The method used to terminate the pregnancy must depend on the severity of the disease and the condition of the patient. In the acute, fulminating type of toxemia occurring in primiparas, cesarean section is usually the method of choice. Even in some multiparas with acute exacerbation of symptoms and an unfavorable cervix, cesarean section may be indicated. In milder cases and even in severe cases in multiparas in which the cervix is favorable, rupture of the membranes and delivery from below may be the best procedure. However, each case must be judged by itself, and the attending obstetrician should take the whole situation into consideration before making his decision.

Eclampsia

Eclampsia is the final stage of an unchecked pre-eclampsia. Many cases of pre-eclampsia are not sufficiently severe to develop into eclampsia, but many other cases do, if not properly treated. Eclampsia is the development of convulsions or coma, or both, following pre-eclampsia. Not all cases of coma or convulsions in pregnancy are due to eclampsia. Among the causes of convulsions that must be differentiated from eclampsia are epilepsy, hysteria and diabetes. Also, various cerebral lesions must be ruled out. The convulsions of eclampsia may appear before, during or after labor. Typically, a patient has a series of convulsions separated by periods of lethargy. Accompanying the convulsions is marked hypertension and albuminuria. Casts — hyaline, epithelial and granular — may appear in the urine. There is a marked reduction in the output of urine and sometimes complete suppression. DeLee[8] gives the maternal mortality of eclampsia as 13 per cent, with a fetal mortality of 40 per cent.

The treatment of eclampsia should be preventive. The uterus should be emptied before the convulsions appear. Once the convulsions have appeared, the treatment is primarily conservative. On the basis of the original Stroganoff treatment, sedation and rest are the primary objectives. The patient should be put in a quiet and dimly lighted room. The eyes should be covered, and the ears blocked with cotton. She should be well sedated with morphine and chloral hydrate. Chloroform is still used to control the convulsions. Magnesium sulfate may be given intravenously in a 20 per cent solution. Hypertonic glucose may be administered intravenously to stimulate kidney excretion. Veratrone is recommended by Kellogg.[21] Willson[22] states that the administration of veratrone causes a marked suppression of urine in pre-eclampsia. Dieckmann[9] warns of the danger of vascular collapse from this drug.

The treatment of the disease is the fundamental problem in eclampsia, and no attempt at delivery should be made during the convulsive stage. Cesarean section is definitely contraindicated. Frequently, labor begins, and delivery is normal. In other cases, when the convulsions are under control, labor may be induced, and the patient allowed to progress through labor. Rupture of the membranes is the simplest and surest way of induction, and the use of the bag is not recommended. The patient often shows some improvement after the rupture of the membranes. The labor should be allowed to proceed at its own speed, and no interference should be considered until the cervix is fully dilated. Frequent complications of eclampsia are anuria, pulmonary edema and sepsis.

The end results of pre-eclampsia and eclampsia show permanent damage in many cases. According to Kellogg[21] the residual lesion from the former is hypertension, which was found in 50 per cent of cases. After eclampsia, hypertension was present in 60 per cent. Glomerulonephritis did not occur in any patient as the result of eclampsia. The older the patient, the greater the parity, the higher the blood pressure during pregnancy and the longer the duration of the illness, the greater the liability to the ultimate occurrence of hypertension.

Dexter and Weiss[1] believe that hypertension follows toxemia of pregnancy in 25 per cent of patients who have had a normal blood pressure before pregnancy, and an elevation in the percentage of women who have had hypertension before pregnancy. The occurrence of sustained post-partum hypertension depends more on the duration than on the severity of the toxemia. Sustained hypertensive vascular disease may be initiated by toxemia of pregnancy.

Reid and Teel[23, 24] report that in 235 cases previously diagnosed as mild pre-eclampsia, six months to three years after delivery, no patients had renal impairment. In 21 per cent the systolic pressure was over 150. Of 89 patients with hypertension before pregnancy, 44 per cent had a higher blood pressure six months to three years after delivery than when first seen.

Browne and Dodds[25] report 400 toxemic patients studied six to twelve years after delivery. Fifty-one per cent had hypertension. They found, as Kellogg did, that older patients with greater parity, higher blood pressure and longer duration of illness were more likely to develop hypertension. There were no cases of glomerulonephritis as a result of toxemia. Sixty per cent of the patients had hypertension after eclampsia. The authors suggest that patients who develop residual hypertension after pre-eclamptic toxemia and eclampsia have a familial tendency to the disease, which pregnancy has merely revealed. The onset of pregnancy hastens the disease, which sets in at an earlier period than it would otherwise have done.

Summary

Essential hypertension of the benign type is not seriously influenced by pregnancy. There is a greater incidence of pre-eclamptic toxemia in these patients than in normal pregnant women. A superimposed toxemia is a serious danger.

Pregnancy is a dangerous complication of renal disease, resulting in increased kidney damage. Superimposed toxemia increases this damage. Pregnancy should not be permitted in severe renal disease.

Pre-eclamptic toxemia is best treated by proper prophylaxis. Excessive weight gain is a predisposing cause. If the toxemia does not respond to medical treatment, the uterus should be emptied before convulsions develop.

Eclampsia should be treated conservatively.

Permanent hypertension after toxemia has a definite relation to the length of time the disease persists, as well as to its severity.

References

1. Dexter, L., Weiss, S., et al. *Preeclamptic and Eclamptic Toxemia of Pregnancy.* 415 pp. Boston: Little Brown & Co., 1941.
2. Grollman, A. *Recent Progress in Hormone Research.* New York: Academic Press, Inc., 1947.
3. Smithwick, R. H. Experiences with surgical treatment of hypertensive cardiovascular disease in man. *Cleveland Clin. Quart.* **12**: 105-117, 1945.
4. Newell, J. L., and Smithwick, R. H. Pregnancy following lumbodorsal splanchnicectomy for essential and malignant hypertension and hypertension associated with chronic pyelonephritis. *New Eng. J. Med.* **236**:851-858, 1947.
5. Sharkey, J. A., and Hess, C. B. Effect of essential hypertension on pregnancy. *Am. J. Obst. & Gynec.* **52**:672-676, 1946.
6. Chesley, L. C., Annitto, J. E., and Jarvis, D. G. Study of interaction of pregnancy and hypertensive disease. *Am. J. Obst. & Gynec.* **53**:851-863, 1947.
7. Stander, H. J. *Textbook of Obstetrics: Designed for the use of students and practitioners.* 1277 pp. New York: D. Appleton-Century Co., 1945.
8. DeLee, J. B., and Greenhill, J. P. *The Principles and Practice of Obstetrics.* Ninth edition. 1011 pp. Philadelphia: W. B. Saunders Co., 1947.
9. Dieckmann, W. J. *The Toxemias of Pregnancy.* 521 pp. St. Louis: C. V. Mosby Co., 1941.
10. Eastman, N. J., and Steptoe, J. J., Jr. Management of pre-eclampsia. *Canad. M. A. J.* **52**:562-568, 1945.
11. Cosgrove, S. A., and Chesley, L. C. Management and treatment of late toxemias of pregnancy. *Am. J. Obst. & Gynec.* **51**:67-74, 1946.
12. Colvin, E. D., and Bartholomew, R. A. Behavior of basal metabolism in course of developing toxemia of pregnancy: correlation with cholesterol, placental infarcts and retinal examination. *Am. J. Obst. & Gynec.* **37**:584-604, 1939.
13. Smith, O. W., Smith, G. V., and Hurwitz, D. Increased excretion of pregnanediol in pregnancy from diethylstilbestrol with special reference to prevention of late pregnancy accidents. *Am. J. Obst. & Gynec.* **51**:411-415, 1946.
14. Smith, O. W. Menstrual toxin. I. Experimental studies. *Am. J. Obst. & Gynec.* **54**:201-211, 1947.
15. Cosgrove, S. A., and Chesley, L. C. Management and treatment of late toxemias of pregnancy. *Am. J. Obst. & Gynec.* **51**:67-74, 1946.
16. Hertig, A. T. Vascular pathology in hypertensive albuminuric toxemias of pregnancy. *Clinics* **4**:585-614, 1945.
17. Tenney, B., Jr. Syncytial degeneration in normal and pathologic placentas. *Am. J. Obst. & Gynec.* **31**:1024-1028, 1936.
18. Tenney, B., Jr., and Parker, F., Jr. Placenta in toxemia of pregnancy. *Am. J. Obst. & Gynec.* **39**:1000-1005, 1940.
19. Bell, E. T. Renal lesions in toxemias of pregnancy. *Am. J. Path.* **8**:1-42, 1932.
20. Ingerslev, M., and Teilum, G. *Year Book of Obstetrics and Gynecology.* Chicago: Year Book Publishers, Inc., 1946. P. 105.
21. Kellogg, F. S. Toxemias of pregnancy. *Clinics* **4**:585-647, 1945.
22. Willson, J. R. Action of veratrone on blood pressure, urine volume and urea clearance in toxemias of pregnancy. *Am. J. Obst. & Gynec.* **49**:665-672, 1945.
23. Reid, D. E., and Teel, H. M. Nonconvulsive pregnancy toxemias: their relationship to chronic vascular and renal disease. *Am. J. Obst.* **37**:886-896, 1939.
24. Teel, H. M., and Reid, D. E. Eclampsia and its sequelae: clinical and follow-up study of all cases at Boston Lying-In Hospital over 20-year period. *Am. J. Obst. & Gynec.* **34**:12-25, 1937.
25. Browne, F. J., and Dodds, G. H. Remote prognosis of toxaemias of pregnancy. *J. Obst. & Gynaec. Brit. Emp.* **46**:443-461, 1939.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 34011

Presentation of Case

A seventy-eight-year-old man entered the hospital complaining of an ache in the abdomen of three weeks' duration.

For six weeks he had noted ankle edema. Soon he developed swelling of the abdomen, anorexia, mild abdominal distress, exertional dyspnea, and watery, black stools four times a day. In this period he lost 8 pounds. Previously his health had been excellent. He denied orthopnea, chest pain, cough, jaundice or excessive alcohol intake. He admitted taking a glass of wine with meals. For six months the patient had suffered from incontinence, frequency, nocturia, weak stream and difficulty initiating the stream.

Physical examination revealed a well developed but emaciated, elderly man in no distress. No jaundice was noted. A Grade I aortic systolic murmur was heard. Abdominal examination showed ascites, a liver edge palpable 3 cm. below the costal margin and slightly tender, bilateral inguinal hernias, hemorrhoids and a prostate one and a half times the normal size. There was +++ pitting edema of the ankles and lower legs.

The temperature, pulse and respirations were normal. The blood pressure was 175 systolic, 85 diastolic.

Examination of the blood disclosed a red-cell count of 5,900,000, with 16.5 gm. of hemoglobin, and a white-cell count of 8400, with a normal blood smear. The urine contained no albumin, sugar or bile, and had a specific gravity of 1.020. Two stools were guaiac negative. The total protein was 5.96 gm. per 100 cc., with an albumin-globulin ratio of 1.41. The nonprotein nitrogen was 30 mg. and the cholesterol 156 mg. per 100 cc., the cholesterol esters being 85 mg. per 100 cc. The prothrombin time was 27 seconds (normal, 17 seconds), and the

cephalin-flocculation test + in twenty-four and +++ in forty-eight hours.

A barium-enema examination was negative. Chest films showed collapse of the right upper lobe, which contained multiple small cavities. There was old pleuritis at the right base and apex. The trachea and upper mediastinal structures were displaced to the right.

Paracentesis produced 3230 cc. of bloody fluid with 430,000 red cells and 150 white cells per cubic millimeter and a specific gravity of 1.010. No tumor cells or tubercle bacilli were found in the ascitic fluid.

Cystoscopy showed no cause for the urinary symptoms except a slightly enlarged prostate.

The patient became quite jaundiced, and the ascites recurred. On the fifteenth day bleeding into the skin occurred, and 200 cc. of blood was aspirated from the mouth. He died the following morning.

Differential Diagnosis

Dr. Myles P. Baker: We are dealing with an elderly patient with ascites and ankle edema of relatively short duration (three to six weeks) and a noteworthy absence of symptoms, except for those attributable to prostatic hypertrophy. There was a history suggestive of bleeding from the upper gastrointestinal tract. The important negative findings on physical examination seem to me to be the absence of evidence of congestive heart failure; the absence of any abnormal physical findings, particularly over the right upper lobe; the absence of a palpable spleen or spider angiomas; and also the lack of a really large liver. The liver edge was said to be palpable 3 cm. below the right costal margin, but that is only about two fingerbreadths, if that, and we do not know where the upper border of the liver was. Possibly, the finding represents a low liver rather than a large one. There is no note on rectal examination regarding whether any firm mass was palpable in the rectal shelf. Presumably it was not, or it would have been mentioned. But that is an important finding in an elderly person with ascites.

The laboratory studies revealed certain important features. First of all, there was no anemia — or surprisingly little for a man in whom liver disease is suspected. There was no element of renal insufficiency, which is significant in a man who had been having urinary symptoms that made him uncomfortable rather than ill. There was no bile in the urine, which tallies with the finding of no detectable icterus. We have no evidence on examination for bleeding into the gastrointestinal tract. The serum protein of 5.96 gm. per 100 cc. is barely below the normal range, and the serum albumin can be calculated as ±3.5 gm. per 100 cc., which is slightly below the normal range but not so low as one would expect to be one of the chief causes of a large accumulation of ascitic fluid. The globulin of 2.4 gm. per 100 cc. is at the upper limits of normal and not so high as one would expect in the usual case of cirrhosis of the liver with ascites. The normal blood cholesterol levels are about what one would expect, and I do not quite see why the test was done in the first place. There was no significant decrease in the esterified portion, as one sees with acute liver-cell damage. The prolonged prothrombin time is important, but it was not within the danger level that causes hemorrhage. Finally, the cephalin-flocculation test of +++ in forty-eight hours is consistent with liver-cell damage. The one test that I should expect that the house officers would have recourse to, the bromsulfalein-excretion test, apparently was not done. The finding of bloody ascitic fluid, of course, sticks out in this protocol like a sore thumb. It has always been and is still a very rare finding in cirrhosis of the liver and immediately directs one's attention toward the possibility of a cancerous process involving the peritoneum. X-ray examinations were subsequently done, probably with this in mind. A barium enema revealed no evidence of cancer in the cecum, sigmoid or rectum. X-ray examination of the chest revealed an abnormal finding, a collapsed right lower lobe with multiple small cavities, which I think I shall ask Dr. Wyman to describe.

Dr. Stanley M. Wyman: The collapsed right upper lobe lies in this location at the apex, with what appears to be thickened pleura over the apex. Multiple small areas of decreased density are present that may represent dilated bronchi scattered throughout this rather shrunken lobe. The trachea is deflected considerably toward the right. The right leaf of the diaphragm is moderately elevated, and there is what may be a small amount of fluid or thickened pleura in the costophrenic angle. The heart shadow is retracted a little toward the right, with a prominent left ventricle, a tortuous aorta and some calcification, which is all in keeping with the hypertension. The lung fields, except for the right upper lobe, show no definite localized disease. I can trace the bronchi rather well in both lung fields. I cannot entirely exclude obstruction of the right upper-lobe bronchus, however. A barium enema is described, but I can only find incomplete films of that examination. A gastrointestinal series was apparently done, although we have no report of it, but it may be of help to Dr. Baker. The esophagus can be seen very fragmentarily, and there is no definite evidence of esophageal varices. The stomach appears to be within normal limits. I believe that there is probably an enlarged liver and possibly a large spleen.

Dr. Baker: Do you consider these areas of diminished density in the collapsed lobe compatible with dilated bronchi rather than cavities?

Dr. Wyman: Yes; or they could be small bronchiectatic cavities.

DR. BAKER: In a further search for possible sites of carcinoma, a cystoscopy was done, and apparently carcinoma of the prostate excluded. The patient went on to die in two weeks, a short course of seven weeks' illness in all, with evidence terminally of bleeding in the gastrointestinal tract and the skin, and deepening jaundice — a picture that we consider compatible with a cholemic death. Against the diagnosis of cirrhosis of the liver, again, are the bloody ascitic fluid, the serum albumin level of 3.5 gm. per 100 cc. in the presence of ascites, the absence of anemia, the absence of splenomegaly to be found in probably two thirds of such cases of cirrhosis and ascites and the absence of collateral circulation found in 50 per cent of such cases and of spider nevi. The patient was old for cirrhosis.

The question arises whether the findings in the chest by x-ray examination are compatible with a diagnosis of bronchiogenic carcinoma. I cannot rule out the presence of a bronchostenotic lesion involving the right upper-lobe bronchus. With such a lesion I would expect more evidence of active infection distal to the tumor. However, it is interesting to remember that in bronchiogenic tumors the first symptoms may be those of metastases, distant metastases, rather than mere chest pain and blood-streaked sputum. Bronchiogenic carcinoma frequently metastasizes by way of the blood stream and involves the liver in about 35 per cent and the peritoneum in 4 to 5 per cent, and the abdominal lymph nodes in a third of the autopsy cases. The possibility of such an origin of carcinoma must therefore be borne in mind in this case. I have never seen such a situation, however, — ascites as the presenting symptom with bronchiogenic carcinoma, — possible though it may be, and I could find no reference to it in the literature. I am inclined to look upon the findings that Dr. Wyman has demonstrated in the chest x-ray film as an old story in an elderly man, due probably to inflammatory disease involving the upper-lobe bronchus with atelectasis, representing an inactive process.

The question of a primary hepatoma arises in this patient, who presented grossly bloody ascites, which is a common finding in the presence of this rather rare tumor; probably in two out of three malignant hepatomas such grossly bloody ascites is found. We have very little evidence for the presence of cirrhosis of the liver, which is frequently associated with primary hepatomas, and I think that the absence of such an antecedent history of cirrhosis and of a large, firm, hard liver are rather important points against the diagnosis of hepatoma. It is a rare tumor. Moreover, we have no evidence of tumor elevating the right leaf of the diaphragm — a finding that I have seen in cases of hepatoma. In considering a possible site of origin for what I take to be metastatic carcinoma involving the parenchyma of the liver and peritoneum, I come then by exclusion to carcinoma of the body of the pancreas. The patient had none of the characteristic backache, left sided or midline, that such persons with carcinoma of the body of the pancreas have. This tumor frequently involves the peritoneal surface as well as the liver and gives rise to progressive swelling of the abdomen as the initial symptom, closely followed by edema of the ankles, jaundice and the clinical picture presented in this case. Perhaps chiefly because I have seen it do so, I shall choose it as the most likely diagnostic probability in this man who presented bloody ascites as the outstanding abnormality and who gave, for reasons noted above, no grounds for the diagnosis of cirrhosis of the liver.

DR. CHESTER M. JONES: Is it not true that in the lower film it would be impossible to state that the liver or spleen was enlarged because there is so much fluid and homogeneous density?

DR. WYMAN: Yes.

CLINICAL DIAGNOSIS

Peritoneal carcinomatosis.

DR. BAKER'S DIAGNOSIS

Carcinoma of body of pancreas.

ANATOMICAL DIAGNOSES

Hepatoma, with extension into portal and hepatic veins.
Portal cirrhosis of liver, inactive.
Bronchiectasis, right upper lobe.
Benign prostatic hypertrophy.
Arteriosclerosis, generalized.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: I think that this case is a very blind one from the diagnostic point of view. The diagnosis was established a day or two before death by peritoneoscopy, but we believed that there would be no fun in discussing it if we gave the results of the peritoneoscopic biopsy of the liver. It showed the characteristic picture of hepatoma. At autopsy the right lobe of the liver was completely replaced by tumor, which had invaded extensively both the portal and the hepatic venous systems. This is characteristic of primary liver-cell carcinomas. There were no distant metastases. The spleen was not enlarged, weighing only 170 gm. There were no esophageal varices. There was, however, in the left lobe of the liver, evidence of an old burnt-out cirrhosis, such as is almost invariably found in patients who develop hepatoma. We have had only 1 case in this laboratory of primary liver-cell carcinoma not associated with cirrhosis. That was in a ninety-five-year-old woman. Dr. Kernahan, what is your experience in this regard?

DR. JAMES W. KERNAHAN: We have just gone over our cases of carcinoma of the liver at the Mayo Clinic and found 75 per cent of the hepatomas associated with cirrhosis. Twenty-five per cent were not, but those were usually in children.

DR. MALLORY: Cholangiomas in general are less frequently combined with cirrhosis than the hepatomas.

Two other findings of possible importance were a bronchiectasis in the right upper lobe and a moderate hypertrophy of the prostate.

DR. BAKER: Do you often find pain in the right upper quadrant in patients with hepatoma?

DR. MALLORY: One does, but one also finds pain in the right upper quadrant in patients with cirrhosis who have no tumor. There is no explanation for the pain whatsoever.

CASE 34012

PRESENTATION OF CASE

A nineteen-year-old boy was admitted to the hospital because of difficulty in urination.

Three months before entry he began to notice an "itch" in the anus that gradually changed to a dull ache "inside," above the anus and to the left. This pain was worse on bending over. It finally became so severe that he was unable to lie on his back. One month later, while at work, he had a sudden episode of dizziness and "pins-and-needles" sensation all over. This passed off in an hour but left him weak, and he did not wholly recover for two or three weeks. Eight days before entry he was unable to urinate although the bladder felt distended. He had to be catheterized. Two days later he again was unable to void and had to be catheterized. This time he had severe back pain as well. In the last five days before admission he had difficulty in urination, relieved somewhat by Sitz baths. The back pain was intermittent and associated particularly with retention. He had mild constipation and a weight loss from 135 to 126 pounds in the three-month period. There was no history of frequency, nocturia, stones or venereal disease, no paresthesias of the legs and no disorder of gait.

Physical examination revealed a well developed, nervous, apprehensive boy. He had bilateral, small, soft, palpable, anterior and posterior cervical lymph nodes. There was a left lumbar scoliosis. On rectal examination there was a hard, fixed, irregularly rounded mass about 2 cm. in diameter at the junction of the sacrum and coccyx, to the right of the midline. It was questionably tender. A complete neurologic examination was negative, except that the ankle jerk was less active on the left side.

The temperature was 97°F., the pulse 90, and the respirations 20. The blood pressure was 115 systolic, 60 diastolic.

The white-cell count was 10,000, with 80 per cent neutrophils. The red-cell count was 4,570,000. The fasting blood sugar was within normal limits, and a blood Hinton test and a routine urine examination were negative. The cerebrospinal fluid was acellular, and the protein was 36 mg. per 100 cc.

An intravenous pyelogram showed normal kidneys, with prompt excretion of the dye on both sides. The bladder was large and emptied incompletely. There was no definite abnormality of the pelvis. There was questionable loss of trabeculation of the right distal sacral segments, although this area was partially obscured by bowel contents. A myelogram showed a free flow of Pantopaque from the ninth dorsal body to the cul-de-sac, without evidence of defect. A barium enema showed no intrinsic disease or displacement of the rectum or sigmoid. No mechanical obstruction was seen by cystoscopy or panendoscopy. X-ray examination of the chest was negative.

While in the hospital the patient was treated with tidal drainage of the bladder and sulfadiazine. He had a few episodes of "stabbing pains" just to the left of the anus, radiating anteriorly through the perineum. These were associated with a constant grimace, and he held himself rigid on the left side.

An operation was performed on the fourteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. ROY E. MABREY: This patient presented a history of intermittent pain in the low back extending into the perineum. He also had difficulty in urination. The onset was gradual, and the symptoms increased in severity.

The itch noticed in the anus may have resulted from irritation of a nerve, or it may have been that the patient's attention was drawn to this area. The type of pain characterized by a dull, intermittent ache could have resulted from pressure due to inflammation or to neoplasm.

The episode of dizziness with "pins-and-needles" sensation may have been due to a reflex reaction with a concomitant fall in blood pressure.

The mechanism of emptying the bladder became more and more disturbed. Eight days before admission and again two days later the patient had to be catheterized. There is no note of how much urine was obtained, but analysis was normal when he entered the hospital. An intravenous pyelogram showed no evidence of hydronephrosis, and there was enlargement of the bladder with incomplete emptying. Obstruction to the outflow, such as that due to stricture, stone or an enlarged prostate, would have caused spasm of the bladder and given rise to considerable pain. The atonic nature of the bladder, or the dysuria, points to some involvement of its nerve supply.

Neurologic examination revealed no abnormality, except that the ankle jerk was less active on the left than on the right. There were no sensory changes or disorder of gait. A lumbar puncture revealed normal fluid, but no mention was made of the dynamics. A myelogram was normal, however. These findings tend to eliminate an intrathecal lesion. The change in bowel habit with constipation

was not accompanied by diarrhea, bleeding or tenesmus. It may have been due to restricted food intake and reduced activity.

Physical examination disclosed soft lymph nodes in the neck. The axillas and groins are not mentioned. Examination of the blood showed a white-cell count of 10,000, with 80 per cent neutrophils. This is within normal limits but might point toward an inflammatory process. Other studies, including the sedimentation rate, calcium, phosphorus and alkaline phosphatase, might have been of some help.

On rectal examination there was a hard, fixed, irregularly rounded mass about 2 cm. in diameter at the junction of the sacrum and coccyx. The problem is to determine the nature of this fixed mass, on the assumption that it could account for all the symptoms.

In discussing the possibilities, I should like to list four general headings: congenital, traumatic, infectious and neoplastic.

Spina bifida, the most common of the congenital lesions in this region, would manifest itself at an earlier date and a defect should be noted by x-ray examination. A cyst, such as a dermoid or a teratoma, which often contains teeth or bone, would also show on the x-ray film.

There was no history of injury, and one severe enough to cause these symptoms would have caused other signs.

A perirectal abscess occurs above the levator ani muscles and is quite rare. Also, the patient is likely to have chills and fever with a high white-cell count. Osteomyelitis would give more constitutional reaction, with a high white-cell count. Tuberculosis in this area is rare without widespread involvement. The negative blood Hinton test probably rules out syphilis.

In my opinion the mass palpable on rectal examination was neoplastic in origin. It is not likely that it arose in the rectal wall. There was no ulceration of the mucosa, which would have been accompanied by bleeding and tenesmus. Any ulceration could have been detected with a sigmoidoscope, although barium studies might not have outlined it. A neurogenic tumor has to be considered and cannot be ruled out. Since the tumor arose in the vicinity of the sacrum, primary bone tumors have to be thought of. Although Ewing sarcoma has a predilection for the shaft of long bones and half the cases occur before the age of fifteen years, it may occur in the sacrum and at another age. It is likely to be accompanied by elevation of temperature, and x-ray examination usually shows new bone being deposited in layers. Osteogenic sarcoma may occur in any bone, but it is found most often in the long bones. The greatest incidence is at the age of twenty, and the pain is usually constant; the x-ray findings are more definite than they were in this case. A chondroma or chondrosarcoma is a possibility. Metastatic disease is not likely to produce a single projecting lesion such as this.

There are two tumors left to be considered that are not too infrequent in this area: chordoma and benign giant-cell tumor. Chordoma arises from remnants of the fetal notochord. Its growth is very slow, and pain is the first symptom. A study of 150 cases reported in 1935 revealed that no patient with a chordoma in the sacrococcygeal region sought medical advice in less than four months after onset.* The average age of the patients was fifty years, although 6 cases occurred between twenty and thirty years. Considerable destruction of bone had taken place before the patient consulted a physician.

Giant-cell tumor is usually slowly growing. The presenting symptom is pain, which is intermittent in character. The greatest incidence of occurrence is between the ages of fifteen and twenty-five. Destruction and regeneration of bone give a "soap bubble" roentgenogram.

The presence of intermittent ache and dull pain of three months' duration in a boy of nineteen, with no elevation of temperature, point to a neoplastic process. The interference with bladder function indicates that the growth occurred in proximity of the nerves of the bladder. In the absence of good x-ray films, which are usually very characteristic, I shall put giant-cell tumor of the sacrum as my first choice.

Clinical Diagnosis

Chondrosarcoma of sacrum.

Dr. Mabrey's Diagnosis

Giant-cell tumor of sacrum.

Anatomical Diagnosis

Ewing sarcoma of sacrum.

Pathological Discussion

Dr. Benjamin Castleman: This patient was seen by many consultants, and the consensus was that he had a sacrococcygeal tumor, with chondrosarcoma leading the list. It was not considered advisable to attempt a biopsy through the rectum. The lower half of the sacrum and the entire coccyx were excised en bloc by Dr. W. J. Mixter. When received in the Pathology Laboratory, the specimen showed replacement of a portion of the sacrum by reddish-gray tissue, which on microscopical examination proved to be a Ewing sarcoma.

Although there was no gross evidence of residual disease at operation, tumor was found in the soft tissues microscopically. The patient was therefore given 6000 r of x-ray therapy, 1500 kilovolts over a 15-by-15-cm. field being given during a period of six weeks. When seen two months later, he already had pulmonary metastases.

*Mabrey, R. E. Chordoma: study of 150 cases. *Am. J. Cancer* 25:501-517, 1935.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. — Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. — John Fallon, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. — Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR

EDITORIAL BOARD
C. Guy Lane, M.D. — Harvey R. Morrison, M.D.
Henry R. Viets, M.D. — Maxwell Finland, M.D.
Robert M. Green, M.D. — James M. Faulkner, M.D.
Dwight O'Hara, M.D. — Carroll B. Larson, M.D.
Fletcher H. Colby, M.D. — Francis D. Moore, M.D.
Robert L. Goodale, M.D. — C. Stuart Welch, M.D.
Chester M. Jones, M.D. — Vernon P. Williams, M.D.
Benjamin Castleman, M.D. — Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: $7.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $8.00 per year (Boston funds); $9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

MORE POLIOMYELITIS CRIPPLES

THE statisticians of the Metropolitan Life Insurance Company have just published some interesting figures* that should disperse any doubts in the minds of those who have felt that there is no real need for what they consider the large sums of money solicited and sometimes obtained by the National Foundation for Infantile Paralysis in their annual "March of Dimes." The four years from 1943 through 1946 constitute the longest period of sustained high incidence of the disease in the history of this country. There were more than 25,000 cases in 1946 alone; this number has been exceeded only once before, in 1916, when more than 27,000 cases were reported. As might be expected this recent increase in cases was accompanied by a steady rise in the number of children and young people with crippling impairments resulting from the disease.

Although poliomyelitis may attack persons of any age, children are its chief victims. Only 1 of every 5 patients reported is more than fifteen years old and less than 1 in 10 is over twenty-one. Poliomyelitis is the cause of almost one fifth of all orthopedic handicaps under the age of twenty-one.

The number of children and young people that have been crippled by infantile paralysis has increased 10 per cent in two years and almost 45 per cent in the past seven years. It is estimated that in January, 1947, there were 74,000 persons under twenty-one who were crippled to some degree by this disease, whereas the number at the beginning of 1940 was about 51,000. This is a true increase and not one accounted for merely by an increase in the child population, since the number of crippled survivors rose from 10.6 per 10,000 population in 1940 to 14.4 in 1947, an increase of 36 per cent. Massachusetts has been rather fortunate in this respect, being one of only three states (the others are New Mexico and Maine) in which a drop in the number of crippled survivors has been recorded, the number in Massachusetts having declined 14 per cent between 1940 and 1947. The greatest increases occurred in Utah, Arkansas, Colorado, Ohio, Tennessee and Indiana. The increases for the same period in those states ranged between 230 per cent and 100 per cent in these cases.

On January 1, 1947, the proportion of crippled survivors from poliomyelitis per 10,000 children and young people under twenty-one years of age varied in different states. The highest proportion was in Minnesota, where there were 31 per 10,000 population; in Rhode Island there were 25, in New York state 19, and in Massachusetts 12.5. Other states, like Virginia and Delaware, had about 6.5 cripples per 10,000 children.

The current year shows improvement for the first time in the figures on the incidence of poliomyelitis over recent years. It appears that the record flare-up of the disease that started in 1943 has been broken. Very few localized epidemics have occurred this year, and it is estimated that the total

*Increased toll of cripples from poliomyelitis. *Statistical Bull.* 28:5-8, 1947.

number of cases for the year in this country will be around 10,000, which is considerably less than the figure for any of the four preceding years.

It is true that only a fraction of those attacked by poliomyelitis suffer permanent crippling, and many of those who are actually paralyzed during the course of the disease recover their function fully within a relatively short time. The figures presented by the Metropolitan's statisticians indicate that, nevertheless, there are in this country a considerable number of victims who are left more or less crippled. Unfortunately, there are as yet no preventive measures against the disease. The National Foundation for Infantile Paralysis has provided a large proportion of the funds that have gone into the care and rehabilitation of persons ill with and crippled by this disease. The Foundation also supports a great deal of research bearing directly on poliomyelitis. Those entrusted with the dispersal of funds for the Foundation deserve greatest credit for extending support from these funds in recent years to researches in allied fields of virus diseases. In the long run this is the best means of assuring a supply of trained investigators in the broad field of virus diseases and of advancing knowledge in this general field that will eventually be brought to bear directly on the researches on infantile paralysis. This program offers every reason for hope that poliomyelitis will in time be brought under control.

It is interesting that these data come not from the National Foundation for Infantile Paralysis, but from the statistical department of a large insurance company. Some of those who have doubted that their dimes go to a good cause or that it is necessary to keep up the contributions from year to year need only to make the simple calculations of the costs of maintaining the hospital beds and the follow-up care for the large number of children crippled from poliomyelitis. It must then be obvious that even the largest amounts that have ever been realized in the annual "March of Dimes" and even much larger sums are needed for the proper care of these crippled children and for continuation of the studies in this field. This need will continue for some time to come. Only through a continuing program of researches such as those sponsored by the National Foundation for Infantile Paralysis can we expect to bring about a final solution to the proper management and prevention of this disease and its crippling effects.

SHORTAGE OF NURSES

THERE is general agreement that the shortage of registered professional nurses has reached the critical stage. The plans for voluntary prepaid medical care in effect throughout the country, with the consequent extension of hospital services to ever-increasing numbers of people, have created an unprecedented demand for nurses; enrollment in the Nation's 1227 schools of nursing has not kept pace with this need, although the figure of 40,000 new student nurses in 1947 set a peacetime record.

The extremely serious situation resulting from the shortage has received widespread attention, and many methods of solution have been suggested. One of the most constructive appears to be the campaign of the Student Nurse Recruitment Committee of the American Hospital Association to enroll approximately 50,000 new student nurses in 1948. This drive has the endorsement and support of the Women's Auxiliary of the American Medical Association, the American Dental Association and the National Tuberculosis Association, as well as the co-operation of the National Committee on Careers in Nursing, American Red Cross, American Medical Association and American College of Surgeons.

It must be emphasized that even the most intensive and practical schemes for recruitment will fail unless something is done to deal with the causes of the apparent lack of interest among qualified young women, the foremost of which is the low pay for exacting and onerous duties. The average nurse earns $40 for a forty-four-hour week.[1] When this figure is compared with the wages of workers in industry and considered in the light of the present cost of living, the reason for the shortage is understandable. And when it is realized that nurses have no social security and few of the benefits

accepted as a matter of course among industrial workers, there can be no surprise that young women of high caliber and intelligence are reluctant to go through a period of intensive training to prepare themselves as nurses. All solutions to the problem, therefore, depend essentially on the fact that the nursing profession must be made more attractive.

Thus, physicians can do much to influence qualified young women in their choice to enter this most vital profession, and efforts on the part of women's auxiliaries can be equally effective. But nurses must first be accorded the recognition and benefits commensurate with their professional status; certainly, they are justified in demanding the rights taken for granted by even unskilled workers — better pay for fewer hours of work, social security, sick leave, vacation pay and adjustment for night and overtime work. Suggestions of substituting practical nurses for registered professional nurses to take over the major part of ordinary bedside care[2] and for greater utilization of nurse's aides offer some hope for a solution of the problem, although such proposals appear to underestimate the danger of nursing care of inferior quality at a time when the public is demanding the highest standards in all forms of medical care. Finally, Congress must be persuaded to continue the exemption, inaugurated during the war years and permitting registration of nurses at the age of twenty, to the requirement of a minimum age of eighteen years set by the Board of Registration of Nurses for admission to nursing schools. But even girls who graduate from high school at the age of seventeen could not be blamed for seeking professions offering better pay and better working conditions than those offered by a nursing career.

Physicians and their wives are urged to make every possible contribution to the campaign of the Student Nurse Recruitment Committee. The medical profession and hospital administrations are also urged to co-operate by exerting every effort to obtain for nurses their proper recognition and economic stability.

References

1. Editorial. Forceful challenge. *New York Herald Tribune*. November 29, 1947.
2. Fishbein, M. Nursing as career. *Hygeia* 25:915, 1947.

LIQUIDATION OF THE EMERGENCY MATERNITY AND INFANT CARE PROGRAM

A NOTICE elsewhere in this issue of the *Journal* calls attention to the liquidation of the Emergency Maternity and Infant Care Program in the United States. In Massachusetts there are many outstanding physicians' bills, some dating back to the beginning of the program. It is important that all outstanding medical bills be submitted immediately. The expanded staff necessary to carry this program is now being contracted because of the cessation of administrative funds; therefore, it will become increasingly difficult, and will take a longer time, for approval and payment of bills. It is to the physician's own interest to render his bills as soon as possible.

ROBERT N. NYE MEMORIAL FUND

The American Cancer Society, Incorporated (Massachusetts Division), announces that the Robert N. Nye Memorial Fund is in excess of $2385.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CURTIS — Charles L. Curtis, M.D., of Salem, died on December 11. He was in his sixty-second year.

Dr. Curtis received his degree from Bowdoin Medical College in 1909. He was for many years senior member of the surgical staff at the Salem Hospital, and was a fellow of the American College of Surgeons and the American Medical Association and a member of the New England Surgical Society.

A daughter, two sons and several grandchildren survive.

GREENWOOD — Arthur M. Greenwood, M.D., of Boston, died on December 14. He was in his seventy-first year.

Dr. Greenwood received his degree from Harvard Medical School in 1902. He was formerly a member of the staffs of the Massachusetts General, New England Deaconess and Palmer Memorial hospitals. He was a member of the New England Dermatological Society, American Dermatological Association and American Academy of Dermatology and Syphilology and was a fellow of the American Medical Association.

His widow and two stepsons survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

LIQUIDATION OF EMERGENCY MATERNITY AND INFANT CARE PROGRAM

Physicians who have outstanding bills for pediatric and obstetric care given to Massachusetts mothers and children under the Emergency Mater-

nity and Infant Care Program are urged to submit these bills for payment, immediately, since the program is now in the process of liquidation.

A separate bill and a statement of services rendered must be submitted for each patient for whom compensation has not been received. If necessary, additional copies of the required blank forms that must be completely filled out by the physician — "Physician's Statement of Obstetric Services Rendered" or the "Physician's Statement of Pediatric Services Rendered" — may be obtained from the Division of Maternal and Child Health, 73 Tremont Street, Boston. The bill must be presented on the physician's regular, printed statement form.

STATE PLAN FOR THE ADMINISTRATION OF HOSPITAL SURVEY AND CONSTRUCTION ACT

The State Plan for the administration of Public Law 725 (Hospital Survey and Construction Act) has been approved by the State Advisory Council and the Public Health Council of the Massachusetts Department of Public Health and, following a public meeting on November 12 in Boston, by the Surgeon General of the United States Public Health Service.

In the Massachusetts Plan, existing general hospitals were distributed among seventy service areas. The most recent survey of hospital beds in Massachusetts indicates that there are 18,224 general-hospital beds, 1,100 beds for patients with chronic diseases, 3,604 beds for patients with tuberculosis and 21,102 beds for mental patients. In accordance with the federal formula as given in Public Law 725, the number of beds needed according to the categories mentioned above is, respectively, 23,829, 9,136, 4,408 and 22,840.

A priority schedule based primarily on the percentages of need met by existing facilities was established, and all general hospital construction will take place in accordance with this schedule. Top rank in the list was given to seven hospital areas within the Commonwealth — namely, Athol, Needham, Medford, Northbridge, Woburn, Milford and Ipswich. It is expected that within the first year of the program it will be possible to make two or three grants among the applicants having a Group A priority.

An allotment will also be designated for the construction of hospital units for chronic diseases. The metropolitan areas of the Commonwealth, including Boston, Springfield, Worcester and Pittsfield, will have first priority in this category. Finally, 20 per cent of the total allotment for the first year will be allocated for the construction of health centers.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER, 1947

Résumé

Diseases	November 1947	November 1946	Seven-Year Median
Chancroid	5	2	2*
Chicken pox	753	770	1025
Diphtheria	18	61	17
Dog bite	636	664	631
Dysentery, bacillary	21	3	22
German measles	60	63	59
Gonorrhea	234	378	378
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	0	1*
Malaria	5	15	15
Measles	153	691	691
Meningitis, meningococcal	5	6	12
Meningitis, Pfeiffer bacillus	3	5	5
Meningitis, pneumococcal	4	1	4†
Meningitis, staphylococcal	1	0	0†
Meningitis, streptococcal	0	0	0†
Meningitis, other forms	0	1	1†
Meningitis, undetermined	7	1	3†
Mumps	461	306	523
Pneumonia, lobar	48	61	193
Poliomyelitis	15	54	24
Salmonellosis	8	14	7
Scarlet fever	305	292	704
Syphilis	235	303	407
Tuberculosis, pulmonary	222	224	217
Tuberculosis, other forms	12	12	16
Typhoid fever	1	2	2
Undulant fever	3	5	4
Whooping cough	648	598	661

*Three-year median.
†Five-year median.

Comment

Diseases with incidence above the seven-year median are diphtheria, dog bite, German measles, salmonellosis and pulmonary tuberculosis.

Diseases below the seven-year median are chicken pox, malaria, measles, meningococcal meningitis, mumps, lobar pneumonia, poliomyelitis and scarlet fever.

Poliomyelitis dropped to less than one third of the prevalence of November, 1946, the peak having occurred nearly a month earlier this year than last.

Although diphtheria did not maintain the sharp upward trend of October, the seasonal increase is certain to continue with a peak some time in December, January or February.

Measles is at the lowest prevalence for November since 1906, and chicken pox at the lowest since 1931.

Geographical Distribution of Certain Diseases

Diphtheria was reported from: Boston, 10; Chelsea, 1; Dedham, 1; Everett, 2; Revere, 2; Somerville, 1; Westminster, 1; total, 18.

Dysentery, bacillary, was reported from: Salem, 3; Swampscott, 1; Waltham, 3; Worcester, 8; Wrentham, 6; total, 21.

Malaria was reported from: Everett, 1; Haverhill, 1; Lynn, 1; Malden, 1; Worcester, 1; total, 5.

Meningitis, meningococcal, was reported from: Brookfield, 1; Cambridge, 1; Hingham, 1; Montague, 1; Quincy, 1; total, 5.

Meningitis, Pfeiffer bacillus, was reported from: Cambridge, 1; Holyoke, 1; Leominster, 1; total, 3.

Meningitis, pneumococcal, was reported from: Boston, 1; Cambridge, 1; Everett, 1; Quincy, 1; total, 4.

Meningitis, staphylococcal, was reported from: Chelsea, 1; total, 1.

Meningitis, undetermined, was reported from: Agawam, 1; Chicopee, 1; Haverhill, 1; Holden, 1; Holyoke, 1; Hopedale, 1; Worcester, 1; total, 7.

Poliomyelitis was reported from: Agawam, 1; Brookline, 2; Dighton, 1; Easthampton, 1; Gloucester, 1; Ipswich, 1; Lynnfield, 1; Malden, 1; Newton, 1; Milford, 1; Salem, 2; Somerville, 1; Wenham, 1; total, 15.

Salmonellosis was reported from: Ipswich, 1; Lynn, 1; Malden, 1; New Bedford, 1; Norwood, 1; Peabody, 1; Worcester, 2; total, 8.

Septic sore throat was reported from: Amesbury, 1; Boston, 4; Cambridge, 1; Greenfield, 1; Montague, 1; Warren, 1; total, 9.

Tetanus was reported from: Great Barrington, 1; total, 1.

Trichinosis was reported from: Lawrence, 1; Lenox, 4; Lowell, 1; Pittsfield, 1; total, 7.

Typhoid fever was reported from: Boston, 1; total, 1.

Undulant fever was reported from: Avon, 1; Boston, 1; Dalton, 1; total, 3.

MISCELLANY

UNFILLED VACANCIES IN HEALTH DEPARTMENTS

Unfilled professional vacancies in state and local health departments of twelve States, totaling 590 more than in 1945, were disclosed recently when the Committee on Training of Public Health Personnel, United States Public Health Service, Federal Security Agency, announced the results of a spot survey made last spring. The Committee conducted the survey in April, 1947, as a follow-up of a compilation made in July, 1945, when 38 state and 930 local health departments reported a total of 2593 vacancies in nineteen categories of full-time positions and 2000 positions being held for persons in the armed services. Although incomplete information was supplied by eight of the twelve states queried last spring, a total of 1847 unfilled jobs were reported in the same nineteen categories for which the twelve states recorded 1257 vacancies in July, 1945. Replies from these states indicated that the impact of medical men returning from military duty had not yet been felt. In thirteen of the nineteen types of positions, vacancies reported in 1947 were greater than those in July, 1945. Prominent totals among unfilled positions in the twelve States checked last April were: health officers, 117 (55 in 1945); medical officers, 186 (101 in 1945); graduate nurses, 940 (654 in 1945); and sanitary and public-health engineers, 81 (36 in 1945). The states included in the spot survey were: California, Colorado, Georgia, Illinois, Kentucky, Louisiana, Massachusetts, Michigan, Minnesota, New York (exclusive of New York City), North Carolina and Texas.

ASSOCIATION OF STATE AND TERRITORIAL HEALTH OFFICERS

At the annual meeting of the Association of State and Territorial Health Officers, held recently in Washington, D. C., the following officers of the Association were elected: president, Dr. Vlado A. Getting, of Massachusetts; vice-president, Dr. R. L. Cleere, of Colorado; and secretary-treasurer, Dr. L. E. Burney, of Indiana. The Executive Committee members for 1948 include Drs. Getting and L. E. Burney and Dr. R. R. Cross, of Illinois, Dr. P. E. Blackerby, of Kentucky, and Dr. F. C. Beelman, of Kansas.

UNITED STATES PUBLIC HEALTH SERVICE RESEARCH FELLOWSHIPS

Research fellowships for the support of research workers in the medical and related sciences have been made available by the United States Public Health Service. Three types of fellowships are awarded. A predoctorate research fellowship, carrying yearly stipends of $1200 for successful applicants without dependents and $1600 for those with dependents, in addition to tuition fees, which are paid by the United States Public Health Service, is available to qualified applicants with a Bachelor's degree who wish to conduct research at the Bachelor level and to medical students who, having completed one or two years of medical school, wish to spend additional time in a basic science (such as biochemistry, physiology and physics) before completing their studies toward the M.D. degree. A predoctorate research fellowship, carrying yearly stipends of $1600 for successful applicants without dependents and $2000 for those with dependents, in addition to tuition fees, is available to qualified applicants with a Master's degree who wish to conduct research at the Master level and to medical students who, having completed one or two years of medical school, wish to spend additional time in a basic science before completing their studies toward the M.D. degree. A postdoctorate research fellowship, carrying yearly stipends of $3,000 and $3,600, respectively, for doctors without and those with dependents, is available to qualified applicants with a Doctor's degree in medical or related fields, an increase of $300 each year being granted to fellows who are reappointed. And a special research fellowship, which does not carry a set stipend but is determined in the individual case, is available to applicants who qualify for a postdoctorate fellowship and, in addition have demonstrated outstanding ability or who possess specialized training for a specific problem.

The fellowships are awarded for one-year periods and may be renewed. Except in unusual circumstances, postdoctorate fellows are not reappointed for a third year. Applications are acted upon and awards made at intervals of approximately three months.

Application forms and further information may be obtained from the Division of Research Grants and Fellowships, National Institute of Health, Bethesda 14, Maryland.

CORRESPONDENCE

COMMENTS ON FOLIC ACID

To the Editor: It was with considerable interest that I read your editorial entitled "Folic Acid" in the February 6 issue of the *Journal*. Since at the time I had been using the vitamin for over a year and had no less than 75 patients under treatment, I was especially impressed by your statement that "folic acid as a practical therapeutic agent does not, however, directly provide 'new hope for anemics,'" and that the possible benefit of the "oral therapy" might lead to "neglect of therapy," which is a definite disadvantage.

I have tried, therefore, to restrain myself from the exaggerated optimism and enthusiasm that often accompany the introduction of a new therapeutic agent and have been carefully watching the results with an unprejudiced mind for over two years.

Just now, when our series of sprue patients treated with folic acid is over 100, I have read your second editorial, entitled "A Warning Regarding the Use of Folic Acid," which appeared in the November 6 issue of the *Journal* — the same issue in which Sargent's review, "Folic Acid: Pteroylglutamic acid and related substances," is presented.

Although Sargent finishes his paper with the statement that "because a full clinical trial has not been made, it is too early to venture an opinion on the final place of this nutrient in therapeutics," you end the editorial by stating: "Consequently the use of folic acid as a therapeutic agent appears to offer no new benefit but only risk to the patient."

In pernicious anemia, the risk appears to be the alarming incidence of reported neurologic relapses or progression of pre-existing neurologic lesions, sometimes with an explosive onset and spread. Two cases of sprue have been noted by Ross in the United States in which neurologic lesions occurred during folic acid therapy. Of three possible mechanisms of folic acid action on the neurologic disturbances, you mention that the nutrient "may actually exert a positively deleterious influence on the nervous system."

We agree with Sargent that a more exact definition of the clinical entities being studied is essential for the just appreciation of the real effect of therapy. We have seen cases treated for sprue, both here and abroad, that did not fulfil the most important criteria for diagnosis. Two years ago, at one of the clinics of the postgraduate courses sponsored by the American College of Physicians, in a Boston hospital, we were shown the case of an aged woman physician suffering from sprue, who failed to respond to the oral administration of folic acid. The diagnosis was based on steatorrhea and hypochromic anemia.

We have not yet observed the development of neurologic disturbances in sprue during folic acid therapy. The only patient showing typical signs of combined-system disease as pointed out by Suárez, Spies and Suárez ("The Use of Folic Acid." *Ann. Int. Med.* 26:643, 1947) had the condition before the vitamin was started; the question whether it was a case of sprue or of pernicious anemia is still unsettled.

In going over our cases, we can say that the hematologic response of sprue patients to folic acid is as good as that observed with liver extract, but the improvement in their gastrointestinal manifestations is more striking. A number of patients who had been maintained on parenteral liver therapy and were changed to oral folic acid are today — over a year later — in the same, or better, condition than when the change was made.

It is a fact that the response of sprue to folic acid may be facilitated by an accompanying adequate diet, but the same thing holds true for liver extract.

We have yet to see, in this part of the world, any harmful effect that could be attributed to the administration of pteroylglutamic acid.

R. M. Suarez, M.D.

Hospital Mimiya
Avenida de Diego 301
Santurce 29, P. R.

BOOK REVIEWS

Neuropathology in its Clinicopathologic Aspects. By I. Mark Scheinker, M.D. With a foreword by Tracy J. Putnam, M.D. 8°, cloth, 306 pp., with 208 illustrations. Springfield, Illinois: Charles C Thomas, 1947. $6.75.

This short book on neuropathology emphasizes the more frequent diseases of the nervous system — those likely to be encountered in the practice of medicine. The material is designed for the practitioner; many of the finer details of neuropathology and descriptions of the rarer conditions have been either abbreviated or left out altogether. The diseases considered are presented in an excellent, clear style; the case histories are brief and add to the value of the book in view of its primary aim. The illustrations are well produced, although many of them lack the fine details of delineation associated with most books on the subject. The bibliography and index are adequate. In spite of the fact that there are many books available on the subject, this volume should be considered useful in its limited field.

A Prelude to Modern Science: Being a discussion of the history, sources and circumstances of the "Tabulae Anatomicae Sex" of Vesalius. By Charles Singer and C. Rabin. Publications of the Wellcome Historical Medical Museum. New Series, No. 1. F°, cloth, 58 pp., with 59 illustrations. Cambridge: Cambridge University Press, 1946.

This folio volume, dedicated to D'Arcy Thompson and Charles Sherrington, is a discussion of the history, sources and circumstances of the six anatomic tables of Vesalius, first published in 1538, the precursors of his *De Fabrica Corporis Humani* of 1543 and a prelude to all modern science. The authors seek by their study to display some of the forces that converge to make Vesalius a figure of such scientific importance as the father of modern anatomy and some of the currents of sixteenth century thought that enter into his work.

In the *Tabulae* of 1538 renaissance classical scholarship was grafted on medical tradition. Renaissance art was late in influencing anatomy. The *Tabulae* of Vesalius contained the first attempt to represent the vascular system by drawing, but graphic anatomy soon destroyed astrologic medicine. The *Tabulae* themselves, like incunabula, were printed from wood blocks. The first three, drawn by Vesalius himself, illustrate the Galenic physiology of the liver and portal system, of the liver and venae cavae and of the heart and arterial system. The last three, representing the anterior, lateral and posterior aspects of the skeleton, with many postural faults, were drawn by van Calcar, an inferior pupil of Titian.

Born at Brussels in 1514 and educated at Louvain, Vesalius went in 1533 to Paris, where Sylvius (Du Bois) had begun teaching in 1531; Estienne, though ten years older than Vesalius, did not take his medical degree until six years later. Vesalius began to dissect at Paris for Gunther, but returned in 1536 to Louvain, where he dissected his first female body and found a corpus luteum, and in the same year prepared his first complete skeleton.

In 1537 Vesalius went to Italy, where his chief predecessors had been the humanist-anatomists Valla of Venice, Benedictus of Padua, Benevieni of Florence and Gerbi and Achellini of Padua and Bologna. The first early Italian illustrated anatomies to appear were those of Berengar of Capri, about 1520, and Massa of Venice in 1536.

The authors further describe Galenic physiology and its Latin presentation, and discuss certain anatomic elements in the *Tabulae* constituting ideal material for the study of renaissance anatomic vocabulary, which consists of classical and semitic elements in about equal parts. The Hebrew and Arabic influences in anatomic nomenclature are studied in detail, particularly the passage of Arabic terminology to the Latin West.

Finally, the authors translate into English, with learned commentary, the entire Latin text of the *Tabulae*, including a discussion of many of the associated Arabic, Greek and Hebrew terms, and at the end of the volume the six *Tabulae* and their accompanying text are reproduced in facsimile reduction to about half diameter. Besides the *Tabulae* this volume is illustrated with fifty-nine figures reproduced from various medieval sources, and concludes with four indexes respectively in English, Greek, Arabic and Hebrew. It is a memorable and monumental work of scholarship, and a priceless treasure to all students and teachers of anatomy and of medical history.

Cineplasty. By Henry H. Kessler, M.D., Ph.D. With a foreword by Ross T. McIntire, Vice-Admiral (MC), U.S.N., the Surgeon General, United States Navy. 8°, cloth, 201 pp., with 199 illustrations. Springfield, Illinois: Charles C Thomas, 1947. $6.75.

This book is written by the foremost authority and advocate of cineplastic amputations in the United States. He outlines its history and early attempts and then discusses the indications and technic for this procedure in both the upper and the lower portions of the arm. The aftercare and the rehabilitation of the patient are discussed in detail. This is an excellent monograph, well written and well illustrated. It should be in the hands of all surgeons who perform amputations.

Arthritis and Related Conditions. Edited by Theodore F. Bach, M.D. 8°, cloth, 472 pp., with 139 illustrations. Philadelphia: F. A. Davis Company, 1947. $6.50.

Bach has attempted to write a concise, readable book for the general physician. This book was begun by the late Dr. R. Garfield Snyder, whose contributions have been retained for the most part. The book begins with an excellent résumé of the history of arthritis. Diagnostic aids are then evaluated. Special chapters are contributed by well known men. The book gives a practical, concise picture of the various forms of arthritis and their treatment. It is unfortunate that the author uses many old pictures, borrowed from exhibits of the American Rheumatism Association in the early part of the past decade. Many of the other pictures are not clear. More and better pictures would have greatly improved the teaching value of this book. One would prefer to see the usually accepted nomenclature, rather than "atrophic" and "hypertrophic arthritis," used. The book can be recommended as a good review of knowledge, with adequate directions for treatment for the general physician.

The Engrammes of Psychiatry. By J. C. Nielsen, M.D., and George N. Thompson, M.D. 8°, cloth, 509 pp., with 28 illustrations. Springfield, Illinois: Charles C Thomas, 1947. $6.75.

With this book the authors have provided a new treatise, which differs from others because of its basic underlying principles. The volume is a presentation of psychiatric material, seen in the light of neurologic and bioanatomic concepts. It is, as the authors state, "a system of biological psychiatry where the Engrammes — the neuronal patterns of normal and abnormal thoughts and behavior are delineated, gathered and systematized." This approach is fully elaborated in the first part, in which the various concepts of consciousness, emotions, perception, recognition and so forth are exposed against a background of neuroanatomic and physiologic knowledge.

The clinical part of the work, however, is somewhat uneven; in some chapters, as in the one on schizophrenia, the psychopathology of the disturbance is too briefly surveyed and quite superficially handled. The authors claim not to have had any desire of bringing new theories or new dynamics of interpretation of mental diseases into this book, but simply to present all the psychiatric material that can be supported by physiologic explanation. The chapter on psychosomatic medicine seems to be up to date and constitutes a reference that is not found in previous textbooks of this type. The didactic material is interspersed with many clinical cases — most of them personal experiences of the authors — and some of them worth being remembered.

The style is easily phrased and, for this reason, understandable by the average student; a good sized bibliography gives possibility of further reference in many of the topics discussed.

Deep Analysis: The clinical study of an individual case. By Charles Berg, M.D. (Lond.), D.P.M. 8°, cloth, 254 pp. New York: W. W. Norton & Company, Inc., 1947. $3.50.

This book is devoted to the psychoanalytical study of one case. The work is divided into three parts, which are entitled "Part I, Father," "Part II, Mother" and "Part III, Son." In Part I, a glimpse of the technic and method of procedure is given. Transference takes place, and the emergence of a father fixation is also seen in this section. Part II consists of further interviews and the emergence of the mother fixation from beneath the father fixation. In Part III, the subject gains psychologic emancipation, and the author makes a point of stating, "Life has to be lived to be known and the analytical amelioration has to be experienced to be appreciated." How successfully the subject was emancipated after his analysis may be gauged by the author's statement: "He [the subject] had inherited life, and life was already in the process of inheriting him."

The patient displayed many interesting symptoms but during free association he made statements that gave the impression that he had read a number of Freud's works. An attempt has been made by documenting these interviews to give the reader insight into the patient's emotional structure and the mechanisms of his psychic patterns. The book, in the reviewer's opinion, is mainly of interest to the psychiatrist engaged in practicing psychoanalytical therapy.

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held on Tuesday, January 13, at the Massachusetts General Hospital. A symposium will be presented by the Department of Psychiatry of Harvard Medical School.

PROGRAM

4:45–6:15 p.m., in the Bigelow Amphitheater of the White Building:

Problems in Psychotherapy. Stanley Cobb, M.D.
Procedures in Psychotherapy. Jacob E. Finesinger, M.D.
Some Contributions of Social Sciences. Erich Lindemann, M.D.

6:30 p.m. Supper, in East Pay Cafeteria, White Building.

8:00 p.m., in Lower Out-Patient Amphitheater.

Studies with Adreno-cortico-trophic Hormone in Psychoneurotic Patients. Harley C. Shands, M.D., Frederick C. Bartter, M.D., and Gregory Pincus, Sc.D.
A Study of the Levels of Consciousness in Pentothal Anesthesia. Henry W. Miles, M.D., and John H. Tucci, M.D.
Some Physiologic Mechanisms Underlying the Electrical Activity of the Brain. Mary A. B. Brazier, Ph.D., and Jacob E. Finesinger, M.D.

Subsequent meetings will be held on February 10, March 9, April 13 and May 11.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Bigelow Amphitheater of the White Building, Massachusetts General Hospital, on Tuesday, January 13, at 8:00 p.m. Dr. John Hugh Tucci will speak on the subject "Pentothal Narcosis and Succinate."

Physicians and medical students are invited to attend.

FIRST INTERNATIONAL POLIOMYELITIS CONFERENCE

The National Foundation for Infantile Paralysis has announced that it will sponsor the first International Poliomyelitis Conference at the Waldorf-Astoria Hotel, New York City, from July 12 to 17. The State Department has been requested to transmit invitations to more than sixty foreign governments to send official delegates to the conference. These officials will be asked to present summarizations of the problems of poliomyelitis in their countries at a special session. The presiding officer at this session will be Thomas Parran, M.D., surgeon general of the United States Public Health Service.

The program will include scientific and technical papers on research and treatment of poliomyelitis to be presented by professional authorities in the field from this country and abroad. In addition, there will be panel discussions on the various subjects.

Headquarters have been established in the Waldorf-Astoria Hotel under the direction of Stanley E. Henwood, of Chicago, who has been appointed executive secretary of the conference. Arrangements for the conference will be directed from there by Mr. Henwood. In addition to the sessions, there will be scientific exhibits, demonstrations of muscle testing and treatment procedures, and a film program.

MISSISSIPPI VALLEY MEDICAL SOCIETY 1948 ESSAY CONTEST

The Eighth Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1948. The society will offer a cash prize of $100, a gold medal and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents of the United States. The winner will be invited to present his contribution before the thirteenth annual meeting of the Mississippi Valley Medical Society to be held in Springfield, Illinois, September 29 and 30 and October 1, 1948, the Society reserving the exclusive right to first publish the essay in its official publication — the *Mississippi Valley Medical Journal* (incorporating the *Radiologic Review*). All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5000 words, and must be received not later than May 1, 1948. The winning essay in the 1947 contest appears in the January, 1948, issue of the *Mississippi Valley Medical Journal*. Further details may be obtained from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W. C. U. Building, Quincy, Illinois.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC.

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, February 6, 1948.

Arrangements will be made, so far as is possible, for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held May 16–22, 1948, in Washington, D. C. Notice of the exact time and place of the Part I and II examinations will be sent all candidates well in advance of the examination date.

For further information and application blanks address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

POSTGRADUATE ASSEMBLY IN ENDOCRINOLOGY

The Association for the Study of Internal Secretions announces a Postgraduate Assembly in Endocrinology to be held in Los Angeles from February 23 to 28. Applications should be sent to Dr. E. Kost Shelton, chairman, Committee on Postgraduate Instruction, 921 Westwood Boulevard, Los Angeles 24, California.

(*Notices continued on page xi*)